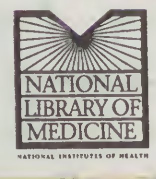
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BOLETIN



"El fumador tiene una probabilidad de más del doble de morir prematuramente que el no fumador".



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CONTENIDO

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Rosa Pérez Perdomo MD, PhD

En el artículo "Dejar de Fumar" que aparece en esta edición se presentan datos de los impactos negativos del fumar, sus efectos fisiopatológicos en el organismo y se repasan algunas de las estrategias y terapias más frecuentemente utilizadas para dejar de fumar. Nos hacemos eco de dicho artículo. Ha sido ampliamente demostrado que la conducta personal juega un papel fundamental en la morbilidad y mortalidad prematura de las enfermedades crónicas. Se ha reportado que el riesgo relativo (RR) de muerte prematura en hombres fumadores comparado con no fumadores es 2.34, es decir, el fumador tiene una probabilidad de más del doble de morir prematuramente que el no fumador (1). Además, se ha demostrado que el fumar interactúa con ciertas exposiciones ambientales y ocupacionales para producir multiplicidad del efecto.

El fumar, como muchas otras conductas o hábitos, tiene una compleja interrelación de factores bioquímicos, sociales, políticos y personales. Aun cuando desde 1988 el cirujano general de los EE.UU. concluyó que el uso de nicotina llena los criterios de dependencia a drogas, una considerable proporción de la población continúa con esta adicción (2). Datos del "Behavioral Risk Factor Survey", encuesta realizada por el Centro de Prevención y Control de Enfermedades (CDC por sus siglas en inglés) para monitorear la prevalencia de las conductas de riesgo asociadas con morbilidad y mortalidad prematura entre adultos (desde 1994 incluye todos los estados, el Distrito de Columbia y Puerto Rico), nos evidencian que en 1998, en la Isla, 15.7% de los encuestados se identificaron como fumadores actuales (3).

Todos estos datos nos señalan que el fumar es una adicción cuyo efecto nocivo en la salud de la comunidad y el correspondiente impacto económico en los servicios de salud es de una gran proporción. Es necesario reforzar una serie de medidas que pueden contribuir a la reducción del consumo. Entre éstas hay medidas legislativas, educativas, diseminación de propaganda, prohibición de fumar en lugares públicos y programas de intervención farmacológica para dejar de fumar.

Creemos que en Puerto Rico se debe enfatizar la necesidad de crear programas comprensivos para controlar la adicción al fumar y, más importante aún, para prevenirla. Entre ellas se debe resaltar la vigilancia epidemiológica que permitiría poder monitorear los grupos y conductas de alto riesgo, el consumo y su tendencia, así como las opiniones de los afectados. De igual forma, se debe apoyar la investigación que ayude a la detección, prevención y diagnóstico de enfermedades e incapacidades relacionadas con el fumar. Para esto es de primordial importancia la intervención del médico para ofrecer ayuda a la persona que quiere dejar de fumar.

En los últimos años hemos visto la proliferación del uso de cigarro o puro, estando esta forma de consumo de "moda" entre diversos sectores de nuestra sociedad. Lamentablemente, esta práctica producirá su impacto en la salud de los consumidores así como en el costo de los servicios de salud, ya sea en un futuro cercano o dentro de algunos años. Es nuestra obligación, como médicos, contribuir a que esta situación se reduzca. Se invita a los colegas médicos a colaborar activamente en lograr que sus pacientes dejen de fumar.

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Artículos de Revisión:

Primary and Secondary Prevention of Cardiovascular Disease in the Elderly

Mario R. García-Palmieri, MD

Cardiovascular disease is the leading cause of death worldwide in populations older than 65 years of age (1). The number of persons constituting the elderly population (aged 65 and over) will increase considerably in the early part of the new millenium for which it is important to give attention to the health care of this population.

Fifty percent of the coronary deaths occur in individuals older than 65 years, with Coronary Heart Disease (CHD) responsible for one half of all deaths in the population older than 85 years of age (2).

In the United States 50% of the individuals aged 55-65 years have hypertension at levels above 140/90 mmHg. At age 65-74 years, 64% are hypertensives. The figures in Puerto Rico are unknown but there is no reason to suspect that they are much different.

The promotion of cardiovascular health in the elderly requires emphasis on the adoption of primary and secondary prevention measures using both non-pharmacologic and pharmacologic interventions.

Primary prevention in cardiovascular disease refers to those measures taken to avoid the development of cardiovascular disease in a healthy individual. *Secondary prevention* refers to those measures taken to avoid the recurrence of cardiovascular events or the occurrence of cardiovascular death in individuals in which cardiovascular disease is already present.

Until recently, landmark studies of hypertension, lipids, exercise and preventive approaches have been focused predominantly on morbidity and mortality benefits accrued to middle-aged males, providing little attention to addressing elderly adults similarly. Recently, attention has been provided to the possible institution of preventive cardiovascular measures at all ages, including the elderly, based upon information obtained in different trials which have included patients older than 65 years of age. The main trials concerning cardiovascular health have been focused on hypertension and coronary heart disease, the two main problems of the elderly cardiovascular patient.

As illustrated in figure 1, in illnesses, there is a pre-disease state that causes changes in the body tissues that generates the disease that we recognize either by clinical findings or by autopsy when death occurs. In CHD the pre-disease state is constituted by the risk factors that cause atherosclerosis (the tissue changes) that leads to the illness which is identified clinically by angina or myocardial infarction or by cardiovascular death corroborated at autopsy. ***Primary prevention*** is instituted by avoiding or controlling the risk factors that cause atherosclerosis and the ***secondary prevention*** is guided, in the presence of atherosclerosis, to the avoidance on the recurrence of angina, myocardial infarction or the ocurrence of cardiovascular death. ***Primary and secondary prevention*** of cardiovascular diseases in the elderly are based upon the detection and control of the recognized risk factors. It includes non-pharmacologic as well as pharmacologic measures.

In the paper we will summarize the available up-to-date preventive measures on the two main cardiovascular problems in the elderly, hypertension and CHD.

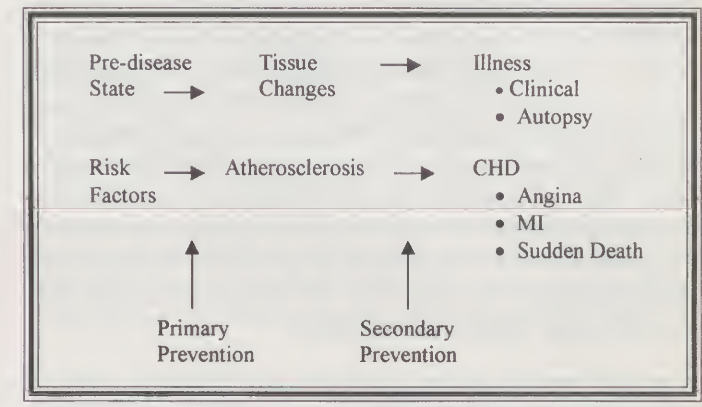


Figure 1. Prevention of Coronary Heart Disease

HYPERTENSION

In the 1970s elderly individuals who had systolic hypertension were often left untreated because of the prevailing impression that treatment was not helpful

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and could cause damage by reducing perfusion of the heart, brain or kidney. The major experimental efforts in the 1980s was directed at demonstrating the efficacy of treating hypertension in younger adult populations. With efficacy demonstrated in younger persons, attention has been directed more recently at the role of blood pressure lowering therapy in reducing mortality and morbidity in the elderly, a segment of our population with a high prevalence of hypertension (3).

The Framingham Study has revealed those women in the 65-74 age group with blood pressure at or above 160/95 mm Hg develop 8 times more fatal cardiovascular events as compared to the normotensives. In men the risk increases 2.4 times, so it is important to control systolic and diastolic hypertension in the elderly.

Primary Prevention - The main primary preventive measures for elderly healthy persons to avoid the development of hypertension consist of life style modifications. These are: 1) Maintain ideal weight and lose weight if overweight 2) Avoid salty foods and reduce ingestion of salt, 3) Reduce alcohol ingestion to no more than 1 drink a day, and 4) Exercise 30-45 minutes daily.

Secondary Prevention - The data from multiple clinical trials have proved that treating hypertension in the elderly reduces the incidence of events related to hypertension such as CHD, cerebrovascular disease and heart failure. There are at least eight important trials that have been completed in elderly individuals with hypertension which are identified by the abbreviation of their title, by the place or institutions where conducted, or by the authors. These are the AUSTRALIAN - Australian National Blood Pressure Study (4); EWPHE - European Working Party on High Blood Pressure in the Elderly (5); HDFP-Hypertension Detection and Follow-up Program (6); HTN-Coop-Hypertension-Stroke Cooperative Study Group; MRC-OA-Medical Research Council Trial in Older Adults (7); SHEP-Systolic Hypertension in the Elderly Program (8); STOP-Swedish Trial in Old Patient with Hypertension (9); and the VA Coop-Veterans Administration Cooperative Study.

Table 1 illustrates these main clinical trials conducted in elderly hypertensives. It includes the number of patients, the age groups and the years of follow-up. The number of patients involved were more than 15,000.

Table 2 reveals the per cent reduction of total events of stroke, CHD and all cardiovascular events for the studies listed in Table 1. The data obtained confirms the importance of treating elderly hypertensives as a secondary prevention measure for reducing the occurrence of cardiovascular events.

Trial	No. Patients	Mean Age	Follow-up (yrs)
AUSTRALLKN	582	64	4.4
COOPE & WARRENDER	884	69	4.4
EWPHE	840	72	4.6
		Age Range	
HDFP	2376	60-69	5.0
HTN-Coop	200	60-75	3.0
MRCO-A	4396	65-74	5.8
SHEP	4736	60-80	4.5
STOP	1627	70-84	2.0

Table 1. Trials of Treatment of Hypertension in the elderly.

First line medications for hypertension in the elderly include diuretics, beta-blockers, calcium antagonists, ACE inhibitors and alpha-1 adrenergic blockers. All are well tolerated and effective. There is evidence that elderly patients do not develop more side effects from the use of antihypertensive therapy than younger patients (10).

Non-pharmacologic intervention in elderly hypertensives in the TONE Study including 900 patients has shown that elderly patients can lose weight and reduce salt ingestion as they follow instructions very thoroughly (11). This eliminates the common belief that elderly patients, because of their age, will not follow the physician advises concerning habit change as well as younger patients.

Trials	Events (%)		
	Stroke	Coronary	Cardiovascular
AUSTRALIAN	-34	-19	-24
EWPBE	-36	-20	-34
COOPE & WARRENDER	-42	-15	-23
SHEP	-36	-27	-32
STOP HYP	-47	-13	-40
MRCO-A	-25	-19	-17

Table 2. Percent change in Total Events in elderly hypertensive patients obtained in different trials.

SYSTOLIC HYPERTENSION

Systolic hypertension occurs when the systolic blood pressure is 160 mm Hg or more and the diastolic blood pressure is less than 90 mm Hg. It is a frequent finding in elderly patient due to the hardening of the aorta and a decrease in the elasticity of the large arteries. Without therapy, systolic hypertension is a confirmed risk factor for CHD, stroke and heart failure.

Three placebo controlled outcome trials on antihypertensive drug treatment of isolated systolic hypertension have been published.

These three large studies are: 1) SHEP (8,12), including 4,736 systolic hypertensives with mean age 71.5 years 2) SYS-EUR (Systolic Hypertension in Europe) (12,13) including 4,695 patients, and 3) SYST-CHINA (Systolic Hypertension in China) (12,14) including 1,253 patients age 60 and older. Outrail, active treatment compared with placebo showed a reduced all-cause mortality of 17%, cardiovascular mortality by 25%, and a reduced all cardiovascular end points by 32%, reduced total stroke by 37% and reduced myocardial infarction (including sudden death) by 25% in the treated groups.

The pooled results of these 3 trials with isolated systolic hypertension prove that antihypertensive therapy must be used in the elderly patient as a therapeutic and preventive measure when the systolic blood pressure is higher than 160 mm Hg.

CORONARY HEART DISEASE

Eighty per cent of the deaths due to CHD occur in people 65 years of age or older. Fifty percent of the deaths of people 85 years old and beyond are due to CHD. More than 50% of all cardiovascular deaths beyond the age of 65 are due to heart failure which is mainly caused by the presence of either coronary artery disease, hypertension or both.

Primary Prevention

Primary prevention of CHD in the healthy elderly is accomplished by addressing measures to counteract the risk factors. The Cardiovascular Health Study including 5,888 adults of both sexes 65 years of age or older followed for 4.8 years showed that systolic hypertension and diabetes were the main predictors of myocardial infarction and that uncontrolled hypertension explained 25% of the coronary events (15). Primary and secondary preventive measures concerning hypertension in the elderly, including isolated systolic hypertension, have already been discussed.

Other risk factors of paramount importance in the primary prevention of CHD in the elderly are the levels of total cholesterol and LDL-cholesterol. Coronary events increase with an increase in LDL-cholesterol. Besides the old studies, pointing to the importance of decreasing high cholesterol levels, two important recent trials on primary prevention in this area are most revealing.

The WOSCOPS (West of Scotland Coronary Prevention Study) randomized 6,595 hypercholesterolemic men to pravastatin therapy or placebo and followed for 4.9 years. Pravastatin reduced total cholesterol by 20%, LDL cholesterol by 26% and reduced major coronary events by 31% compared to placebo. All-cause mortality was reduced by 22%. Older patients in WOSCOPS had similar reductions in CHD rates as younger patients (15,16).

The AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) compared the effects of lovastatin with placebo in 5,608 men and 997 women with average cholesterol levels, including 1,416 persons aged 65-73 years (17-18). Lovastatin therapy reduced LDL-cholesterol levels by 25%. After 5.2 years the major coronary events (fatal or non fatal MI, unstable angina, or sudden cardiac death) decreased by 37%. The effect of such treatment in the older group was comparable with the benefit observed in the overall cohort.

The two studies support the concept that cholesterol-lowering is efficacious for primary prevention of coronary artery disease including the elderly patient.

Secondary Prevention

Secondary Prevention in CHD in the elderly is indicated in patients who already have angina pectoris, myocardial infarctions and those who have had aorto-coronary bypass surgery or angioplasty.

It has been demonstrated that cigarette smokers that discontinued the habit had a longer survival time. Cessation of cigarette smoking yields about a 50% decrease in risk of CHD. It also showed that there was an equivalent effect in patients younger or older than 65 years of age. Patients with CHD, irrespective of age, should be advised to discontinue smoking (19).

The Antiplatelet Trialists Collaboration Overview analyzed in 1994 trials with 54,000 patients at high risk (angina, myocardial infarction, stroke, bypass an angioplasty) and aspirin was found to reduce in 25% the risk of myocardial infarct, stroke or cardiac death. It was effective in elderly patients (20). The Cooperative Cardiovascular Project including 10,018 elderly medicine patients above 65 years of age (1,590 of them 85 years of age or older) showed that those receiving aspirin had a 22% lower mortality rate at 30-day follow-up (21). Daily aspirin is a secondary prevention measure that should be used by all these patients.

Since 1981, the BHAT Study and other beta-blockers studies since have shown that beta-blockers are indicated as a secondary preventive measure in patients with myocardial infarction (22). Recently, a study of 3,737 patients with acute myocardial infarction older than 65 years, of which 601 were above age 85, showed a reduced mortality rate at 2 years for those using beta-blockers (23). These results confirm the usefulness of b-blockers in the elderly patient with MI. All patients who have had a myocardial infarction should be on secondary prevention of beta-blockers irrespective of age.

Three large secondary prevention trials using statin agents have been carried out based upon the principle of cholesterol lowering. These are: 1) 4S, Scandinavian Simvastatin Survival Study (24), 2) CARE, Cholesterol and Recurrent Events (25) and 3) LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease (26). The 4S study used simvastatin therapy in 4,444 men and women with CHD and hypercholesterolemia. It included 1,021 patients aged at least 65 years. The total mortality was reduced by 30%, total coronary deaths decreased by 42%, coronary procedures were reduced 37% and major coronary events decreased by 34%. Patients older than 65 years of age taking simvastatin had reductions paralleling those in patients younger than 65.

In the CARE study, patients with CHD and average cholesterol level of 209 mg/dl received pravastatin therapy or placebo. It included 1,283 patients aged 65-75 years. The medication reduced non-fatal myocardial infarction and coronary revascularization procedures by 27%. Older patients in CARE appeared to benefit as much as younger ones from pravastatin therapy.

In the LIPID trial, there was a reduction in total mortality as well as non-fatal myocardial infarction and coronary death for those individuals on pravastatin therapy. The benefits of the drug therapy extended to the subgroup of patients older than 65 years.

The information obtained from these recent clinical trials data justify including cholesterol lowering therapy as a secondary prevention measure in patients up to 75 years of age. In patients beyond that age with CHD, otherwise healthy, cholesterol-lowering therapy can be given serious consideration. There is no reason at all to withhold cholesterol-lowering therapy solely on basis of age. Eleven secondary prevention studies with simvastatin, pravastatin and lovastatin have also shown a secondary preventive effect for stroke in subjects with CHD reducing its occurrence in 29%. Further analyses and clinical investigations have to be done prior to advocating use of stating for stroke prophylaxis in conjunction with secondary prevention.

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel 11) recommends that adults with CHD should have a lipoprotein profile (total cholesterol, LDL-cholesterol and HDL-cholesterol) and be classified by the LDL-cholesterol level in order to decide management. CHD patients should not have a LDL-cholesterol level higher than 100 mg/dl and should receive medication at such level (27).

The benefit of angiotensin converting enzyme (ACE) inhibitors treatment in patients with heart failure are now well established, and all patients with heart failure and left ventricular systolic dysfunction should receive an ACE inhibitor. Recently some trials have also investigated the late use of ACE inhibitors after myocardial infarction. Three of them have revealed significant favorable results (28). The SAVE (Survival and Ventricular Enlargement) trial consisted of 2,231 patients with myocardial infarction under captopril and placebo and showed a 19% reduction in cardiac deaths at 3-year follow-up of those treated (29). The AIRE (Acute Infarction Ramipril Efficacy) trial consisted of 1,986 subjects with myocardial infarction under Ramipril or placebo and showed a 27% reduction in cardiac deaths at 1.5 years (30). The TRACE (Trandolapril Cardiac Evaluation) trial included 1,749 patients with myocardial infarction under Trandolapril and placebo resulted in a 22% reduction in cardiac death at 2 years (31). The risk of reinfarction was reduced in the three studies.

All three trials are quoted in the American Heart Association/American College of Cardiology Practice Guidelines as recommended therapy after acute myocardial infarction. The ACE inhibitor reduced total mortality by 19%, cardiovascular mortality by 21%, and the recurrence of ischemic events requiring revascularization was reduced by 25% over a follow-up period of 42 months. Fifteen per cent of the patients included were over 70 years of age.

DISCUSSION

With heart disease as the main cause of death woldwide, primarily in the elderly population, it is the responsibility of the practicing physician and other health professionals to utilize as many preventive measures as possible in order to deal with this important health problem.

The practice of medicine has improved throughout the years, and today the preventive and therapeutic measures should be based upon evidence-based medicine which relies upon the results obtained in scientifically designed and conducted multicenter clinical trials.

The experience obtained from multiple multicenter clinical research trials have provided us with enough information to be able to take significant steps concerning primary and secondary prevention of cardiovascular diseases. In the recent past, besides the information obtained from middle-aged populations, many studies, including patients 65 years of age or older, have been done permitting us to identify useful primary and secondary cardiovascular preventive measures in the elderly. As CHD and hypertension are the two big offenders in the elderly patients, cardiovascular prevention in this group is primarily addressed to these two problems and their risk factors.

Primary preventive meaures in hypertension include losing weight if overweight, reducing salt and alcohol intake and exercising regularly for 30-45 minutes per day.

Secondary prevention in elderly hypertensives includes, besides life style changes, blood pressure control with medications, individualized to the patient requirements including his co-morbid problems until the blood pressure levels are consistently below 140/90 mm Hg. The same principle of blood pressure control applies to the elderly with isolated systolic hypertesion.

Primary preventive measures for coronary artery disease in the elderly includes discontinuation of cigarrette smoking and exercise 30 to 45 minutes per day at least 4 to 5 times weekly. Healthy habits like having walking breaks at work, using stairs and gardening should be encouraged. Elderly healthy persons with hypercholesterolemia should receive statin therapy to lower the cholesterol and prevent heart disease.

For elderly persons already with definitive CHD as evidenced by angina, myocardial infarction, coronary artery bypass or angioplasty definitive secondary preventive measures should be instituted. All patients should receive daily aspirin in doses of 80-325 mg per day if there is no contraindication. All post-myocardial infarction patients should receive a beta-blockers to be used indefinetely.

The recent clinical trials data also justify the use of cholesterol-lowering drugs (statins) in cases of myocardial infarction as secondary prevention up to age 75. The decision concerning those with CHD beyond that age should be individualized.

Also, as proposed by American Heart Association/American College of Cardiology guidelines, it is recommended to use ACE inhibitors in persons after an acute myocardial infarction to be continued indefinetely in all patients with left ventricular dysfunction.

SUMMARY

Cardiovascular disease is the commonest cause of death and hospitalization in patients 65 years of age or older. The main offenders among the cardiovascular disorders in this age are CHD and hypertension.

Many non-pharmacologic and pharmacologic mesures in the middle-aged persons have confirmed for many years the effectiveness of primary and secondary prevention. Multiple intervention trials in the recent years have also demonstrated the effectiveness of these measures in patients 65 years of age and older.

A summary of the main primary and secondary non-pharmacologic and pharmacologic measures that have been proven to be effective and useful in elderly patients has been presented with particular attention to hypertension and CHD. It also has been demostrated that elderly patients have the capacity to follow the instructions of their physicians and that, as younger patients, they respond to these measures.

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A revolutionary new vaccine

Help prevent invasive pneumococcal diseases

Proven effective in a large-scale clinical trial (N=37,816)[1]

- Efficacy against vaccine serotypes: 100% (95% CI: 75.4% to 100%)
- Efficacy against all pneumococcal serotypes: 90.0% (95% CI: 58.3% to 98.9%)

A favorable safety profile[1]

- In clinical trials (n=18,168), the most frequently reported adverse events included injection site reactions, fever (≥38° C), irritability, drowsiness, restless sleep, and decreased appetite

Challenging the problem of drug-resistant *Streptococcus pneumoniae*

- The 7 serotypes contained in Prevnar™ (4, 6B, 9V, 14, 18C, 19F, 23F) may help protect against 74% of the penicillin-nonsusceptible pneumococcal infections in children <6 years of age in the U.S.[1,2]

Approved for routine administration[1]

- Infant administration at 2, 4, 6, and 12 to 15 months of age

Administration for previously unvaccinated older infants and children[1]

- For infants and children ≥7 months of age, please see Prescribing Information for appropriate dosing schedule





References: 1. Prescribing Information for Prevnar™, Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein). Lederle Laboratories, Pearl River, NY. **2.** Butler JC, Hofmann J, Cetron MS, et al. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. *J Infect Dis.* 1996;174:986-993.

℞ only

For Intramuscular Injection Only

See Prescribing Information for complete summary.

INDICATIONS AND USAGE

Prevnar™ is indicated for active immunization of infants and toddlers against invasive disease caused by *Streptococcus pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). The routine schedule is 2, 4, 6, and 12-15 months of age. This vaccine is not intended to be used for treatment of active infection. As with any vaccine, Prevnar™ may not protect 100% of individuals receiving the vaccine. For additional information on usage, see DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication to use of this vaccine. Although a severe or even a moderate febrile illness is sufficient reason to postpone vaccinations, minor illnesses, such as a mild upper respiratory infection with or without low-grade fever, are not generally contraindications.

WARNINGS

THIS VACCINE WILL NOT PROTECT AGAINST *S. PNEUMONIAE* DISEASE OTHER THAN THAT CAUSED BY THE SEVEN SEROTYPES INCLUDED IN THE VACCINE, NOR WILL IT PROTECT AGAINST OTHER MICROORGANISMS THAT CAUSE INVASIVE INFECTIONS SUCH AS BACTEREMIA AND MENINGITIS.

Do not give to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer this vaccine to children with coagulation disorders, it should be given with caution. (See DRUG INTERACTIONS.)

Immunization with Prevnar™ does not substitute for routine diphtheria immunization. Healthcare professionals should prescribe and/or administer this product with caution to patients with a possible history of latex sensitivity since this packaging contains dry natural rubber.

PRECAUTIONS

Prevnar™ is for intramuscular use only and SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY. The safety and immunogenicity of other routes of administration (e.g., subcutaneous) have not been evaluated.

General

CARE IS TO BE TAKEN BY THE HEALTHCARE PROFESSIONAL (HCP) FOR SAFE AND EFFECTIVE USE OF THIS PRODUCT.

1. PRIOR TO ADMINISTRATION OF ANY DOSE OF THIS VACCINE, ASK THE PARENT OR GUARDIAN ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS OF THE VACCINE RECIPIENT. THE HCP SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH THIS VACCINE AND TO ALLOW AN ASSESSMENT OF RISKS AND BENEFITS.
2. BEFORE THE ADMINISTRATION OF ANY BIOLOGICAL, THE HCP SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER ADVERSE REACTIONS. This should include a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.
3. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.
4. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children ≥24 months with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised. Data on sequential vaccination with Prevnar™ followed by 23-valent pneumococcal polysaccharide vaccine are limited. In a randomized study, 23 children ≥2 years of age with sickle cell disease were administered either two doses of Prevnar™ followed by a dose of polysaccharide vaccine or a single dose of polysaccharide vaccine alone; safety and immune responses with the combined schedule were similar to polysaccharide vaccine alone.
5. Since this product is a suspension containing an aluminum adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension prior to withdrawing the dose.
6. Use a separate sterile syringe and needle or a sterile disposable unit for each individual to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.
7. Special care should be taken to prevent injection into or near a blood vessel or nerve.

DRUG INTERACTIONS

As with other intramuscular injections, give Prevnar™ with caution to children on anticoagulant therapy.

During clinical studies, Prevnar™ was administered simultaneously with DTP-HbOC or DTaP and HbOC; OPV or IPV; Hep B vaccines; MMR; and Varicella vaccine. (See Prescribing Information for summary of immune response to routine vaccines when administered with Prevnar™.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Prevnar™ has not been evaluated for any carcinogenic or mutagenic potential, or impairment of fertility.

PREGNANCY

Pregnancy Category C

Animal reproductive studies have not been conducted with this product. It is not known whether Prevnar™ can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. Prevnar™ is not recommended for use in pregnant women.

Nursing Mothers

Prevnar™ is not recommended for use in a nursing mother.

PEDIATRIC USE

Prevnar™ has been shown to be usually well-tolerated and immunogenic in infants. The safety and effectiveness of Prevnar™ in children below the age of 6 weeks have not been established. Immune responses elicited by Prevnar™ among infants born prematurely have not been studied.

GERIATRIC USE

Prevnar™ is NOT recommended for use in adult populations. It is not to be used as a substitute for the pneumococcal polysaccharide vaccine in geriatric populations.

ADVERSE REACTIONS

Overall, the safety of Prevnar™ has been evaluated in a total of five clinical studies in which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age. In addition, the safety of Prevnar™ was evaluated in 560 children from four ancillary studies who started immunization at 7 months to 9 years of age. (See Prescribing Information for summary of local reactions and systemic events reported for the efficacy and all ancillary studies.)

The majority of the safety experience with Prevnar™ comes from the Northern California Kaiser Permanente Efficacy Trial in which 17,066 infants received 55,352 doses of Prevnar™ and 17,080 children received a total of 55,387 doses of the control vaccine (investigational meningococcal group C conjugate vaccine [MnCC]), along with other routine childhood vaccines through April 1998. Local reactions and systemic events occurring within 48 hours of each dose of vaccine were ascertained by scripted telephone interview on a randomly selected subset of approximately 3,000 children in each vaccine group. The rate of relatively rare events requiring medical attention was evaluated across all doses in all study participants using automated databases.

For subjects who received Prevnar™ at 2, 4, 6, and 12-15 months of age, the occurrence of local reactions, such as erythema, induration, tenderness, and any interference with limb movement, were described. Additionally, limited data on local reactions in previously unvaccinated older children were described. (See Prescribing Information for complete summary.)

With vaccines in general, including Prevnar™, it is not uncommon for patients to note within 48 to 72 hours at or around the injection site the following minor reactions: edema; pain or tenderness; redness, inflammation or skin discoloration; mass; or local hypersensitivity reaction. Such local reactions are usually self-limited and require no therapy. As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks.

Systemic events included fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, fussiness, and rash or hives. (See Prescribing Information for complete summary.)

The following events were reported within 3 days of a dose during follow-up from October 1995 through April 1998 of the 17,066 subjects who received at least one dose of Prevnar™ in the efficacy trial. There were 24 hospitalizations (for 29 diagnoses) as follows: bronchiolitis (5); congenital anomaly (4); elective procedure, UTI (3 each); acute gastroenteritis, asthma, pneumonia (2 each); aspiration, breath holding, influenza, inguinal hernia repair, otitis media, febrile seizure, viral syndrome, well child/reassurance (1 each). There were 162 emergency room visits (for 182 diagnoses) as follows: febrile illness (20); acute gastroenteritis (19); trauma, URI (16 each); otitis media (15); well child (13); irritable child, viral syndrome (10 each); rash (8); croup, pneumonia (6 each); poisoning/ingestion (5); asthma, bronchiolitis (4 each); febrile seizure, UTI (3 each); thrush, wheezing, breath holding, choking, conjunctivitis, inguinal hernia repair, pharyngitis (2 each); colic, colitis, congestive heart failure, elective procedure, hives, influenza, ingrown toenail, local swelling, roseola, sepsis (1 each).

One case of a hypotonic-hyporesponsive episode (HHE) was reported in the efficacy study following Prevnar™ and concurrent DTP vaccines in the study period from October 1995 through April 1998. Two additional cases of HHE were reported in four other studies, and these also occurred in children who received Prevnar™ concurrently with DTP vaccine.

In the Kaiser efficacy study, seizures were reported in 8 Prevnar™ recipients and 4 control vaccine recipients within 3 days of immunization. Of the 8 Prevnar™ recipients, 7 received concomitant DTP-containing vaccines and one received DTaP. Of the 4 control vaccine recipients, 3 received concomitant DTP-containing vaccines and one received DTaP. In the other 4 studies combined, in which 1,102 children were immunized with 3,347 doses of Prevnar™ and 408 children were immunized with 1,310 doses of control vaccine (either investigational meningococcal group C conjugate vaccine or concurrent vaccines), there was one seizure event reported within 3 days of immunization. This subject received Prevnar™ concurrent with DTaP vaccine.

Twelve deaths (5 SIDS and 7 with clear alternative cause) occurred among subjects receiving Prevnar™, of which 11 (4 SIDS and 7 clear alternative cause) occurred in the Kaiser efficacy study from October 1995 until April 20, 1999. In comparison, 21 deaths (8 SIDS, 12 clear alternative cause, and one SIDS-like death in an older child) occurred in the control vaccine group during the same time period in the efficacy study.

In a review of all hospitalizations between October 1995 and August 1999 in the efficacy study for the specific diagnoses of aplastic anemia, autoimmune disease, autoimmune hemolytic anemia, diabetes mellitus, neutropenia, and thrombocytopenia, the numbers of such cases were either equal to or less than the expected numbers based on the 1995 Kaiser Vaccine Safety Data Link data set.

DOSAGE AND ADMINISTRATION

Vaccine Schedule

For infants, the immunization series of Prevnar™ consists of three doses of 0.5 mL each, at approximately 2-month intervals, followed by a fourth dose of 0.5 mL at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth dose should be administered at least 2 months after the third dose.

Previously Unvaccinated Older Infants and Children

For previously unvaccinated older infants and children, who are beyond the age of the routine infant schedule, the following schedule applies:

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3*
12-23 months of age	2†
≥ 24 months through 9 years of age	1

*2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.

†2 doses at least 2 months apart.

(See Prescribing Information: CLINICAL PHARMACOLOGY section for the limited available immunogenicity data and ADVERSE EVENTS section for limited safety data corresponding to the previously noted vaccination schedule for older children.)

Safety and immunogenicity data are either limited or not available for children in specific high risk groups for invasive pneumococcal disease (e.g., persons with sickle cell disease, asplenia, HIV-infected).

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Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965 U.S.A.
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Estudios Originales:

Cerebral Thrombosis and Vasculitis: An Uncommon Complication of Ulcerative Colitis

María A. Carmona, M.D. Francisco Jaume Anselmi, M.D., F.A.C.P.**, José Ramírez Rivera, M.D., F.A.C.P.****

Abstract: *Cerebral thrombotic disease is a rare and nearly always fatal complication of ulcerative colitis. It is associated with a necrotizing vasculitis. We report a fatal case with a confusing neurologic picture arising from this complication.*

Autopsy revealed necrosis and hemorrhages affecting both cortical grey and white matter. Microscopic examination showed thrombosis of small and medium size vessels associated with hemorrhages and a necrotizing angiitis. Ulcerations, hemorrhages, pseudopolips, and cryptic abscesses were found in the rectosigmoid region of the colon compatible with active ulcerative colitis.

A sudden neurologic deficit in a patient with ulcerative colitis should direct attention to the consideration of a cerebral thrombotic event and the possibility of an associated cerebral vasculitis. Diagnosis may be strongly suggested by MRI or arteriography, but it may require confirmation by biopsy of the brain parenchyma and leptomeninges. A hypercoagulable state has been associated with the thrombosis. Anticoagulation has yielded successful results in some patients with cerebral thrombosis but the risk of massive intracranial and gastrointestinal bleeding preclude to establish clear indications. Neurologic improvement has been obtained with the use of steroids and cyclophosphamide.

Introduction

Thrombotic disease is a rare but nearly always fatal complication of ulcerative colitis. This fatal complication is associated with a necrotizing vasculitis and thrombotic events. We present a 47-year-old man with ulcerative colitis and a confusing neurologic picture arising from this complication.

Case Report

A 47-year-old man developed ulcerative colitis seven years ago. He had been treated periodically for exacerbations, but had not sought medical care or received medications for ulcerative colitis during the previous year. Severe frontal headaches, occasional dizziness, and blurring of vision had been noted during the last four to five years. Two months before admission, occasional shaking chills associated with diarrhea developed. One week before admission, he complained of nausea and was observed to be confused occasionally and forgetful of recent events. Twenty-four hours before admission, he suddenly developed a right hemiparesis and motor aphasia.

On admission, his temperature was 36.7 C, pulse 90 per minute, respiratory rate 20 and blood pressure 110/70 mmHg. He was lethargic and mildly dehydrated. He opened eyes on command but was otherwise unresponsive. The Glasgow coma scale was 7. His head was symmetric with no trauma. The cardiac rhythm was regular and without murmurs. The abdomen was scaphoid and without tenderness, visceromegaly or masses. Bowel sounds were present. Normal pedal pulses were present. Fundoscopic examination showed bilateral papilledema. Direct and consensual pupillary reflexes were absent. Corneal and gag reflexes were present. The right arm and leg were spastic without any spontaneous movement or muscle contraction. The left arm and leg had normal muscle tone. There were no involuntary movements. Brudzinski and Kernig signs were absent. Deep tendon reflexes were hyperactive on the right and decreased on the left.

The white blood cell count was 17,400 cells per cubic millimeters with 28% band forms. The hemoglobin was 11.6 g, the hematocrit 35.5% and the platelet count 181,000 per cubic millimeter. Partial thromboplastin time and prothrombin time were normal. The blood glucose was 176 mg/dl, the albumin 3.1 g. Other serum chemistries were normal. The electrocardiogram showed a normal sinus rhythm and no ST-T abnormalities. A brain CT scan without contrast showed an area of low attenuation extending from the parietal region to the occipital lobe. Midline structures were shifted to the right with compression of the right ventricles. Since findings were suggestive

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of a cerebral tumor, the patient was treated with 300cc of 20% mannitol solution and 10 mg of decadron every six hours, but the neurological status rapidly deteriorated. Within twenty-four hours, obtundation progressed to complete unresponsiveness, and finally coma. The Glasgow coma scale decreased from 7 to 3. Twenty-six hours after admission the patient had a cardiorespiratory arrest and resuscitative measures were unsuccessful.

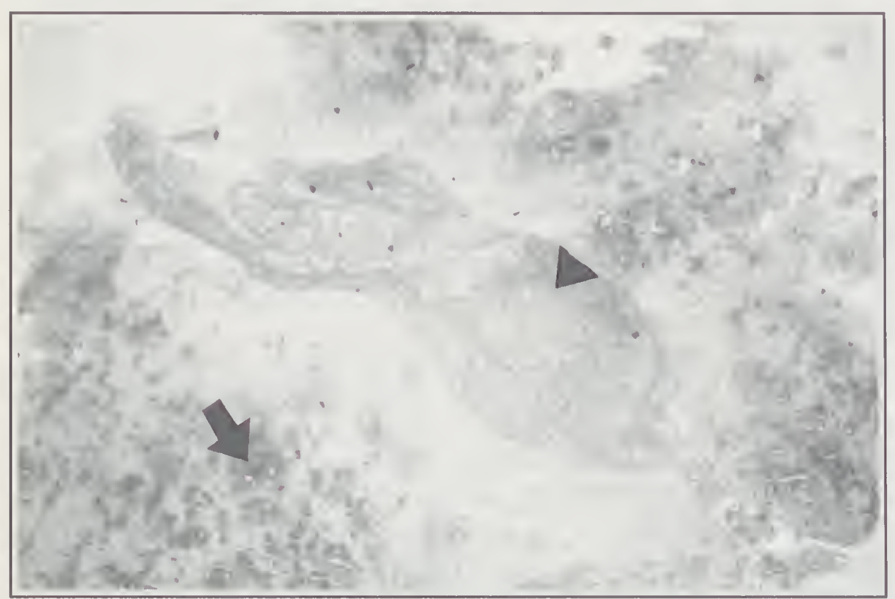


Figure 1. Low power view of the cerebral parenchyma showing thromboses (arrow head) of small and medium size vessels and hemorrhages (arrow). (Hematoxilin and eosin X10.)

At autopsy, the meninges and dural sinuses were free of hemorrhages or thrombosis. The left parietal hemisphere appeared hemorrhagic. Midline structures were shifted to the right. Necrosis and hemorrhages were present in both cortical gray and white matter. Microscopic examination showed thrombosis of small and medium size vessels with associated hemorrhages, (see Fig. 1) and necrotizing angiitis, (see Fig. 2). The rest of the cerebrum showed normal parenchyma, the basal ganglia and spinal cord showed no abnormalities. Stains for herpes simplex types 1&2, and cytomegalovirus were negative. The gastrointestinal tract from cecum to rectosigmoid colon showed shallow ulcerations, intermediate areas of hemorrhages, and pseudopolips. Cryptic abscesses and purulent exudates were also found. Polymorphonuclear cells intermixed with areas of mucosal regeneration suggested an acute inflammatory process.

Discussion

The most likely cause of a sudden neurological deficit in a middle age man with ulcerative colitis is a thrombotic event with cerebral vasculitis. Thrombosis of dural, sagittal, and lateral sinuses have also been reported in patients with ulcerative colitis and also present a similar clinical picture (1). Arterial thrombosis tends to be more common than venous. Active ulcerative colitis needs not to be present in all patients and cerebral thrombosis may occur even after colectomy (7).

Characteristically, the patient has no significant atherosclerosis, hypertension, diabetes mellitus, or any other known risk to predispose to thromboembolic disease (7). This diagnosis may be strongly suggested by MRI or ateriography but it may require confirmation by biopsy of the brain parenchyma and leptomeninges (2).

The mechanism causing the thrombosis is poorly understood. A hypercoagulable state has been described in some of these patients associated thrombosis, elevated factors VII, V, increased fibrinogen, anti-thrombin III deficiency, and transient deficiency of protein C and S.

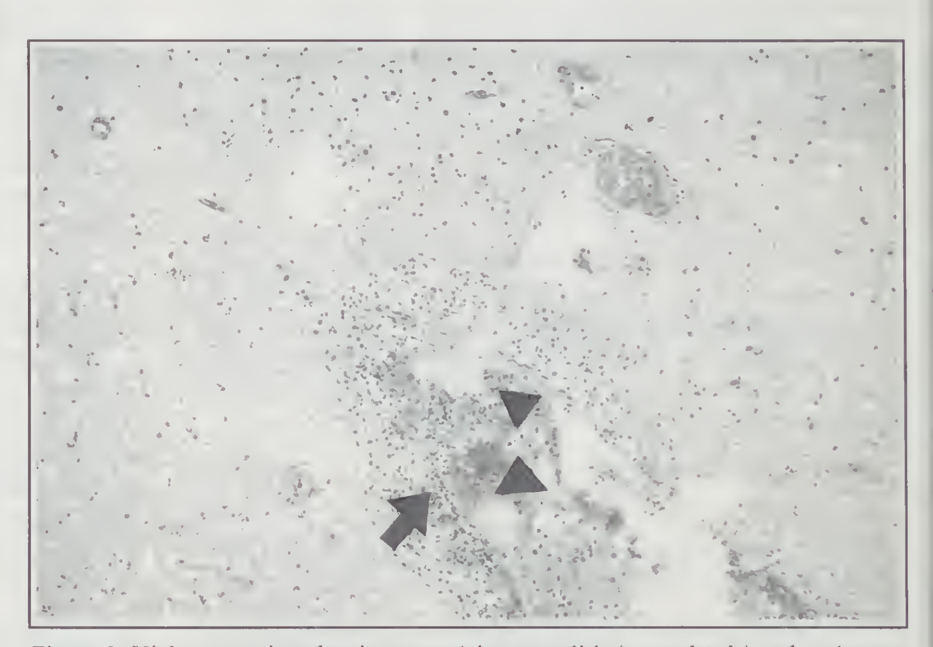


Figure 2. High power view showing necrotizing vasculitis (arrow heads) and an intense inflammatory response (arrow). (Hematoxilin and eosin X 40.)

In others lupus anticoagulant and hyperhomocysteinemia have been identified (5,8,9,6). Endothelial activation by cytokines leading to loss of vessel-wall anticoagulant surface function has been hypothesized (5).

Anticoagulation with heparin, strepto-kinase, and urokinase, have resulted in improvement in some patients but the risk of massive gastrointestinal bleeding has precluded investigations to establish clear indications for anticoagulation therapy (2,4,6,7). In cases where a vasculitis is demonstrated, immunosuppression may be considered. Use of steroids in combination with cyclophosphamide and mesalamine produced neurologic improvement in two reported cases (2).

Resumen: *Enfermedad trombótica cerebral es una complicación rara y casi siempre fatal de colitis ulcerativa. Se asocia además con una vasculitis necrotizante. Informamos sobre un paciente que murió con un cuadro neurológico confuso que surgió de esta complicación.*

La autopsia reveló hemorragias que afectaron la corteza cerebral. El examen microscópico reveló trombosis de los vasos cerebrales medianos y pequeños con hemorragias y una vasculitis necrotizante. Ulceraciones, hemorragias, pseudopólipos, y abscesos crípticos se observaron en la región rectosigmoide lo que sugirió una colitis ulcerativa activa.

Un súbito deterioro neurológico en un paciente con colitis ulcerativa debe dirigir la atención hacia la consideración de un evento trombótico cerebral asociado a una vasculitis cerebral. El diagnóstico se sugiere por estudios de resonancia magnética y ateriografía, pero, en ocasiones es necesaria la biopsia cerebral para confirmar el diagnóstico.. Estados hipercoagulables han sido asociados con la ocurrencia de trombosis. La anticoagulación ha dado buenos resultados en pacientes con trombosis cerebral, pero el riesgo de hemorragias masivas intracranianas y gastrointestinales no ha permitido establecer indicaciones claras. El uso de esteroides y cyclofosfamida ha dado buenos resultados al mejorar el estado neurológico de algunos pacientes.

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Lipitor™ (Atorvastatin Calcium) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases Hypersensitivity to any component of this medication. **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: **Liver Dysfunction** — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively**. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (eg, semiannually) thereafter**. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle — Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class**. Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures)**.

PRECAUTIONS: **General** — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle). ***Antacid:*** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. ***Colestipol:*** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. ***Cimetidine:*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately ***Erythromycin:*** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle). ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. ***Warfarin:*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. ***Other Concomitant Therapy:*** In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS**. Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age. **Geriatric Use**: Treatment experience in adults age ≥70 years with doses of Lipitor up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Lipitor in this population were similar to those of patients <70 years of age.

ADVERSE REACTIONS: Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment:

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment, in <2% of patients treated with atorvastatin in clinical trials.

Body as a Whole: Face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. ***Digestive System:*** Gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** Pneumonia, dyspnea, asthma, epistaxis. ***Nervous System:*** Paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia. ***Musculoskeletal System:*** Leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** Urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia. ***Metabolic and Nutritional Disorders:*** Hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Caution – Federal law prohibits dispensing without prescription.

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Estudios Originales:

Simultaneous Occurrence of Hodgkin's Disease and Chronic Lymphocyte Leukemia: A Unique Presentation

Luis Acaba MD, FACP[1], Deana Hallman MD[1], Edda Rodríguez-Morales MD[2], Román Vélez MD[2] and Enrique Vélez-García MD, FACP[1]

Summary: *Chronic lymphocytic leukemia (CLL) is a chronic, low-grade hematologic malignancy that can transform to a large cell non-Hodgkin's lymphoma (Richter's syndrome), which is associated with an unfavorable prognosis. A distinct Hodgkin's disease subgroup of lymphomatous CLL transformation has been well characterized. We describe a patient presenting with simultaneous manifestations of CLL and Hodgkin's disease. This patient is unique, presenting with separate sites of involvement of each disease within the same organ, in this case the bone marrow. The morphologic and immuno-histochemical findings at diagnosis are correlated with the findings of the postmortem examination.*

Introduction

Chronic lymphocytic leukemia (CLL) is a low-grade, chronic hematologic malignancy with an usually indolent course. In 5-10% of patients there is a well described acute transformation to a large cell non-Hodgkin's lymphoma (Richter's syndrome) which is associated with an unfavorable prognosis (1, 2). A distinct Hodgkin's disease (HD) subgroup of lymphomatous CLL transformation has been described, usually in patients with a known history of CLL (3, 4). When these patients transform, coexpression of HD and CLL in the same anatomical site (composite lymphoma) can occur (5-7). The morphology usually reveals distinct areas of Reed-Sternberg cells in a background of typical CLL (7-9). Rarely patients can also present with coexpression of CLL and HD at diagnosis (6). This then suggests the possibility of either a separate random occurrence of two hematologic malignancies or manifestation of the same related biological phenomenon.

We describe a patient presenting with simultaneous expression of HD and CLL at diagnosis. The patient is unique in presenting with separate and distinct sites of involvement of each disease within the bone marrow. The morphologic and immunohistochemical findings at presentation are correlated with the findings at autopsy.

Case Report

A 58 year-old Hispanic female who was in good health until 5 months before admission when she developed progressive weakness, anorexia and a 30-pound weight loss. Eighteen days before admission she developed nocturnal fever and chills. Physical examination on admission revealed a cachectic female with 38%C temperature. No organomegaly or lymphadenopathy was detected. Complete blood count revealed a leukocyte count of $2.8 \times 10^9/L$, the differential revealing 50% neutrophils, 37% lymphocytes, 12% monocytes, and 1% eosinophils. The hemoglobin was 7.5 g/dL with normocytic indices and the platelet count was $70 \times 10^9/L$. Serum chemistry values revealed an elevated serum calcium level of 14.8 mg/dL and an albumin of 3.0 g/dL. Liver function tests were normal. The chest computerized tomographic (CT) scan revealed a normal sized mediastinum without lymphadenopathy or other abnormalities. Abdominal and pelvic CT scans revealed homogenous splenomegaly and multiple areas of lymphadenopathy in the periportal and retroperitoneal regions. She received packed red blood cell transfusions and aggressive intravenous hydration that resulted in correction of the hyper-calcemia. Parathyroid hormone (PTH) studies revealed a C-term PTH of 68 pg/dl and a PTH-related

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protein of < 0.2 pmol/L, consistent with secondary hypercalcemia. A bone marrow aspirate and core biopsy was performed at the right posterior iliac crest. No aspirable material was obtained from this site ("dry tap"). The biopsy revealed extensive Hodgkin's disease, with both mononuclear lacunar and classic Reed-Sternberg type cells present in a fibrotic, mixed lympho- and histiocytic background. Eosinophils and neutrophils were not prominent. Paraffin immunohistochemical studies were performed on the bone marrow biopsy and demonstrated react-ivity of the Reed-Sternberg type cells with CD 15 with no reactivity to the common leukocyte antigen, CD 45 or to the B-cell antigen CD 20, consistent with the histologic diagnosis of Hodgkin's disease. The surgical consultant felt that the patient's poor physical state precluded an exploratory laparotomy. A second bone marrow aspirate and biopsy was performed on the contralateral (left) posterior iliac crest. The aspirate revealed numerous small mature lymphocytes and the biopsy revealed focal trilineage hematopoiesis with expansion of the marrow interstitium by a monomorphous small lymphocytic infiltrate, both suggestive of CLL. There was no evidence of fibrosis or Hodgkin's disease. Immunophenotyping of the bone marrow aspirate revealed coexpression of CD 5 and B-cell associated antigens (CD 20 and CD 21) in the majority of cells, consistent with the morphologic diagnosis of CLL. CD 11c, an adhesion molecule variably expressed in patients with CLL was observed in the majority of the lymphocytes. This antigen is not expressed in mantle cell lymphoma, an entity that is also CD 5 positive. Concerned over the discrepancy of the bone marrow findings, these were repeated. Again, the findings were consistent with HD in the right iliac crest and CLL in the left iliac crest. Combination chemotherapy with doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) was administered. Six days later the patient awoke lethargic and febrile, the complete blood count revealing a leukocyte count of 0.7×10^9/L, hemoglobin of 7.1 g/dL and platelet count of 14×10^9/L. Multiple packed red blood cell and platelet transfusions were administered but later that night the patient had cardiorespiratory arrest, resulting in her death. Urine culture subsequently revealed the growth of *E coli*. An autopsy was performed which revealed hepatosplenomegaly and generalized lymphadenopathy. Histologic sections of the spleen, liver, bone marrow and lymph nodes revealed a histiocytic background with mild fibrosis, necrosis, and mononuclear and multilobulated large cells suggestive of Reed-Sternberg cells within a generalized monomorphous small lymphocytic infiltrate.

Discussion

Large population-based studies have demonstrated that patients with CLL are at an increased risk for second cancers (3, 10). The various immunologic abnormalities described in these patients may increase their risk of subsequent malignancies (11, 12). The National Cancer Institute's Surveillance Epidemiology, and End Results (SEER) Program detected an almost eightfold risk of HD in patients with CLL, occurring at a median interval of 31 months after the initial diagnosis of CLL (3). A major limitation of this and other older reports has been the lack of immunohistochemical studies. It is known that Reed-Sternberg-like cells, with multiple nuclei and prominent nucleoli are seen in advanced phases of CLL, which makes histologic diagnosis difficult (13). Immunohistochemical as well as histologic evaluation is essential to support the diagnosis. Recent reports using both evaluations have confirmed that HD can develop in patients with preexisting CLL (6, 14, 15).

In this patient, the immunohistochemical finding of CD 15+, CD 45-, and CD 20- in the Reed-Sternberg and lacunar cells at one marrow site confirms the diagnosis of HD, as the CD 15 antigen is not typically expressed in the B-cell of CLL. However the finding of CD 5 (a T-cell antigen) in the small B-cells at the opposite marrow site is consistent with CLL. Yet the autopsy reveals the presence of Reed-Sternberg cells within the small lymphocytes of CLL. How do we reconcile the different bone marrow findings with the results of the autopsy? The distribution of the hematologic malignancies involving the bone marrow is not necessarily homogeneous. Occasionally a marrow sample from one site will not reveal any morphologic abnormality, while malignant cells are evident at the contralateral site. For this reason bilateral sampling of the marrow is usually performed. Since the possible area in the posterior-superior iliac crest where a bone marrow aspiration or biopsy can be performed is limited by anatomy, a repeat bone marrow procedure will be performed in an adjacent site. Due to this, it is not inconceivable that the repeat bone marrow will essentially present similar findings as the original sample.

It is not known if the patient had simultaneous presentation of two unrelated disorders or had transformed from a previously undiagnosed CLL to HD. The former is suggested by the clinical finding of two separate malignancies at diagnosis. Although possible, this would be unlikely by chance alone in two less common malignancies. The latter can occur if one recalls that CLL can be asymptomatic for years during its initial phase, diagnosis only made by a routine blood count. Many patients are therefore diagnosed with advanced disease. Patients with CLL usually present with lymphocytosis, the clinical presentation of leucopenia in the patient suggestive of transformation (Richter's syndrome). Furthermore, the morphologic findings at autopsy of infiltration of lymph nodes, liver, spleen, and bone marrow with Reed-Sternberg-like cells among cells typical of CLL

suggests this transformation of CLL to HD. With the immunohistochemical studies of the bone marrows confirming the presence of both CLL and HD there is little doubt that the Reed-Sternberg-like cells are diagnostic of HD and are not the reactive cells seen in advanced stages of CLL.

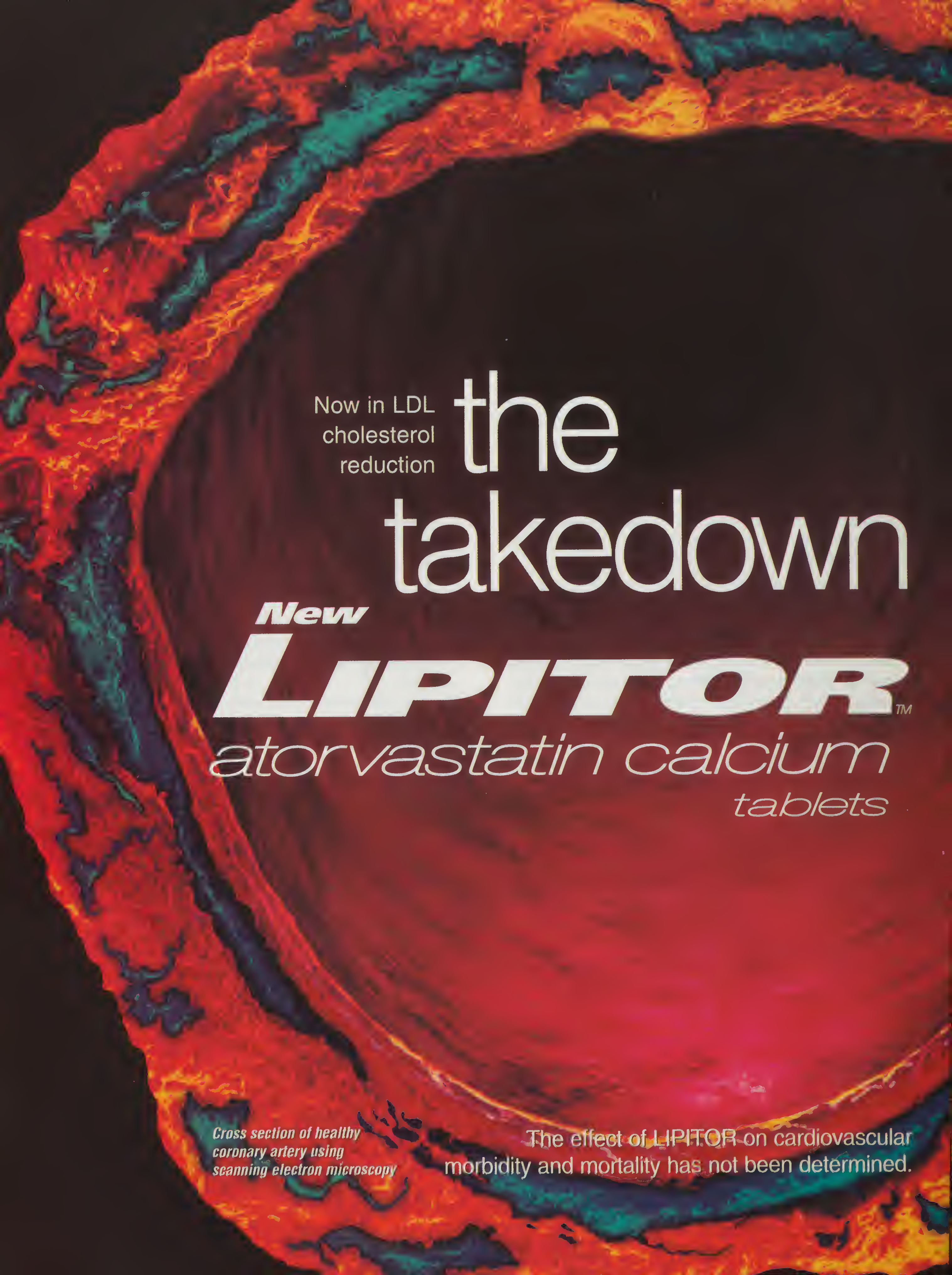
A possible mechanism for the transformation of CLL to HD has been proposed. Momose *et al.* (16) evaluated 13 patients with CLL and coexisting Reed-Sternberg cells. In situ hybridization studies were performed using an oligonucleotide probe complementary to a portion of the Epstein-Barr virus (EBV) gene. In 12 of the cases EBV was identified in the Reed-Sternberg cells but not in the surrounding cells. These findings imply that infection of the malignant B-cells of CLL is perhaps an essential mechanism for the development of HD.

Simultaneous manifestation of CLL and HD at diagnosis has been previously reported, but to our knowledge this is the first reported case with a separate, distinct presentation of each disease within the same organ, in this case the bone marrow. This report also demonstrates the discordance between the clinical diagnoses and the importance of the postmortem examination in reconciling these differences.

Resumen: *La leucemia crónica linfocítica (LCL) es una malignidad hematológica crónica de bajo grado que puede transformarse en un linfoma de non-Hodgkin (Síndrome de Richter), el cual se asocia con una prognosis desfavorable. Hay un grupo de pacientes que transforman de LCL a enfermedad de Hodgkin. Describimos un paciente que presentó LCL y enfermedad de Hodgkin. Este paciente es único en presentar distintos sitios de envolvimiento de ambas enfermedades en el mismo órgano, en este caso la médula ósea. Los hallazgos morfológicos y de inmunohistoquímica se correlacionan con los resultados de la autopsia.*

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LIPITOR is contraindicated in patients with hypersensitivity to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women during pregnancy and in nursing mothers.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of creatine phosphokinase (CPK). Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

*The impact on clinical outcomes of the differences in lipid-altering effects between these treatments is not known. This statement does not compare the effects of LIPITOR 10 mg and higher doses of simvastatin, pravastatin, and lovastatin.



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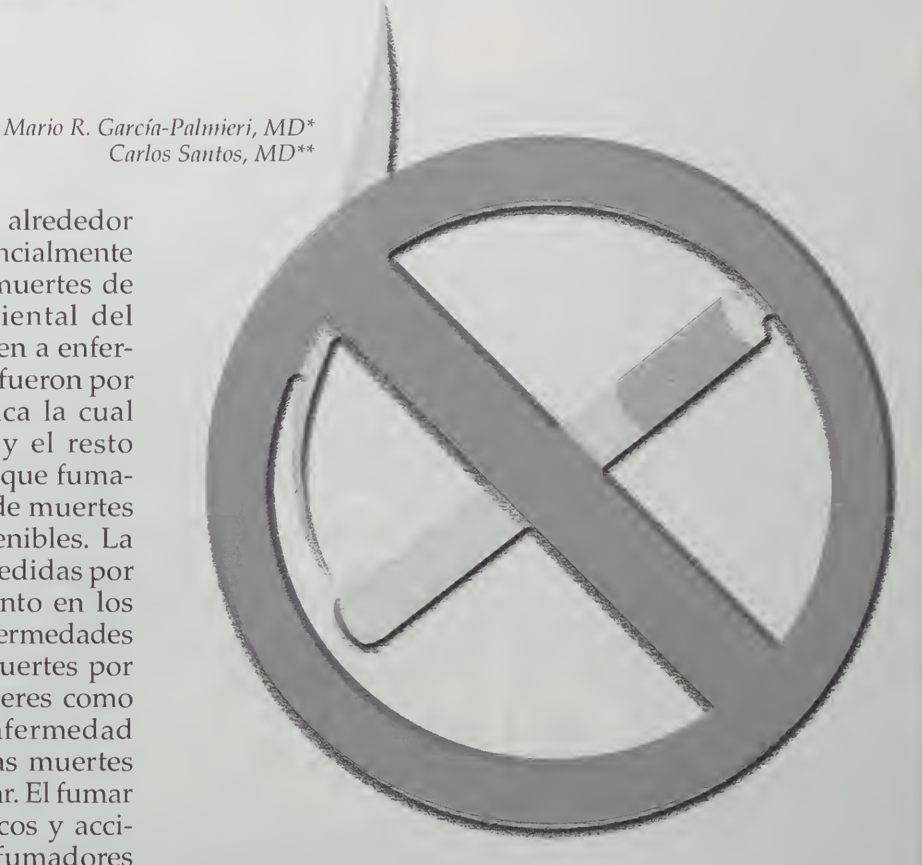
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Artículos de Revisión:

Dejar de Fumar

*Mario R. García-Palmieri, MD**
*Carlos Santos, MD***



El fumar causa en los Estados Unidos alrededor de 430,000 muertes anuales, todas potencialmente prevenibles. Se estiman, además, 40,000 muertes de no fumadores expuestos al humo ambiental del cigarrillo. De éstas, 83,000 muertes se deben a enfermedades respiratorias de las cuales 64,000 fueron por enfermedad pulmonar obstructiva crónica la cual incluye enfisema y bronquitis crónica, y el resto ocurrió por asma y influenza en personas que fumaban. Estas muertes fueron el 5% del total de muertes en la nación y eran potencialmente prevenibles. La gran mayoría de estas muertes fueron precedidas por un largo período de malestar y sufrimiento en los afectados. Además de estas muertes por enfermedades pulmonares, el cigarrillo causó 112,000 muertes por cáncer del pulmón, 31,000 por otros cánceres como los de cabeza y cuello y 201,000 por enfermedad cardiovascular (1). Una quinta parte de las muertes por enfermedades del corazón son por fumar. El fumar duplica el riesgo de sufrir ataques cardíacos y accidentes cerebrovasculares. Uno de cada 10 fumadores habituales desarrolla cáncer del pulmón.

En Estados Unidos hay aproximadamente 15,000,000 de personas con enfermedades respiratorias secundarias al cigarrillo lo cual causa alrededor de 800,000 admisiones a hospitales. Se calcula que las enfermedades relacionadas al fumar cuesta, en cuidado médico, 50 billones de dólares anuales al pueblo norteamericano (datos del "American Heart Association" del 1996).

El fumar tiene efectos devastadores en los pulmones, sin contar los efectos de éste en el corazón, en la presión sanguínea, en el desarrollo de cáncer, incluyendo el del pulmón, el cual es la causa más común de muerte por cáncer en Puerto Rico y Estados Unidos. Sencillamente, el cigarrillo es un factor importante en las muertes por enfermedades cardíacas, cáncer y enfermedades pulmonares, tres de las cinco principales causas de muerte.

En las mujeres embarazadas el fumar es una causa de bebés de bajo peso y de mortalidad prenatal (2). Las mujeres fumadoras tienen más natimuertos, partos prematuros y abortos espontáneos. Los bebés en su primer año de vida desarrollan más pulmonía y bronquitis si sus padres fuman (3, 4). Las madres que fuman 10 ó más cigarrillos al día provocan casos nuevos de asma en sus hijos (5).

El cigarrillo inflama el epitelio del bronquio causando una de dos enfermedades principales: enfisema o bronquitis crónica. El enfisema ocurre por una destrucción del componente elástico de las paredes de los bronquios y los alvéolos causando problemas de obstrucción y pobre intercambio de aire. El aire entra pero no puede salir y queda atrapado en los pulmones. Se diagnostica por los síntomas de falta de aire, cansancio y tos, junto a pruebas de función pulmonar para medir la difusión de monóxido de carbono. La bronquitis crónica ocurre por inflamación de los bronquios e hipertrofia de las glándulas en éstos causando producción excesiva de moco y flema que causa tos y falta de aire. La presencia de tos y expectoración por 3 meses repetida por 2 años consecutivos confirma el diagnóstico.

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Un cigarrillo encendido genera 4000 compuestos entre gases y partículas (6). La nicotina, el monóxido de carbono (gas) y la brea (partícula) son los productos del fumar mejor conocidos. La nicotina es una droga que produce dependencia con un efecto sobre el cerebro y el sistema nervioso. Cuando el fumador inhala, la nicotina va directo a los pulmones y a la sangre y en siete segundos llega al cerebro (7). La nicotina aumenta los latidos del corazón, contrae los vasos sanguíneos y precipita la coagulación de la sangre (8,9). Crea sensaciones de reducción del estrés, de apoyo en momentos difíciles y de bienestar en los momentos de placer. Esto engaña al fumador y le hace más difícil el dejar de fumar.

La situación preocupante de salud y los riesgos que vive el ser humano con el hábito de fumar son reversibles si la persona deja de fumar. El dejar de fumar es una inversión para el futuro: menos tos, menos cansancio, menos ataques cardíacos, menos enfermedades pulmonares, menos cáncer del pulmón, menos muertes y, sobre todo, menos sufrimiento y dolor para la persona.

A pesar de los daños que causa el fumar al ser humano, podemos prevenirlos dejando de fumar, lo cual es algo usualmente difícil para el fumador. El médico y otros trabajadores de la salud tienen que participar activamente en el esfuerzo de sus pacientes para dejar de fumar. Esto conlleva desarrollar una estrategia basada en 4 principios: ***Averiguar, Aconsejar, Ayudar y Arreglos*** (1).

Para los profesionales de la salud trabajar con este problema lo primero por hacer es ***averiguar*** si la persona fuma. Estudios hechos revelan que sólo en el 50% de los expedientes médicos se ha hecho la pregunta al paciente si éste fuma o no. El primer paso es preguntarle al paciente si fuma.

Si el paciente es fumador el segundo paso es ***aconsejar.*** El paciente debe recibir consejería acerca de los beneficios de dejar de fumar, la cual debe ser clara, firme y personalizada. El paciente debe ser educado, sin ser amenazado de los riesgos del fumar para él y su familia. Muchos pacientes inicialmente no consideran parar de fumar, pero se debe establecer un diálogo en encuentros subsiguientes sobre qué piensa hacer con el problema y estimular al paciente a dejar de fumar.

El tercer principio es ***ayudar*** al paciente en el proceso de dejar de fumar. Se establece una fecha para dejar de fumar, usualmente en las subsiguientes dos semanas. Se puede firmar un contrato médico-paciente con el día que se va a dejar de fumar. Se le provee al paciente información acerca de dejar de fumar incluyendo un cassette de motivación, que lo proveen libre de costo muchos programas para dejar de fumar, o literatura de motivación, la cual está disponible a través del Instituto Nacional de la Salud (N.I.H. por sus siglas en inglés). Se determina el grado de adicción a nicotina del paciente para establecer si se va a usar terapia de reemplazo de nicotina tales como la goma de mascar, parchos o el nuevo medicamento, disponible para dejar de fumar, bupropión. Este método se utiliza en pacientes que usan más de una cajetilla de cigarrillos por día, aunque es útil en personas que fumen menos.

Las terapias más comúnmente usadas para dejar de fumar son los parchos de nicotina (Habitrol, Nicorette, Nicoderm, Nicotrol y Prostep), el bupropión (Zyban), y el romper en frío sin terapia para los síntomas de retirada (10, 11). Esta última es la más efectiva donde menos personas recaen, pero pocos pueden lograrlo de esta manera.

Los parchos y otras terapias con nicotina actúan reduciendo la dosis de nicotina paulatinamente y así se evitan los síntomas de retirada de nicotina del paciente. Se usan de seis a diez semanas dependiendo el tipo de parcho, y está prohibido que el paciente fume con el parcho debido a la posible intoxicación con nicotina (efecto aditivo de la nicotina del fumar y el parcho).

El bupropión evita los síntomas de retirada de nicotina en los pacientes. Se utiliza una tableta diaria por tres días y, si es tolerado, se aumenta a una tableta dos veces al día por un período no menor de ocho semanas. Contrario a los parchos, con esta terapia se continúa fumando por ocho días. Siempre se va a parar de fumar el día ocho, y no antes del tratamiento, para dar tiempo para que la medicina obtenga su efecto terapéutico. En estudios recientes ha dado mejores resultados que los parchos, pero se mantiene un alto porcentaje de recaídas debido a otros factores sociales del cigarrillo. Estas terapias deben usarse bajo tratamiento médico.

Una vez establecido el programa para dejar de fumar y el uso de medicamentos, procede el cuarto principio de hacer los ***arreglos*** para darle seguimiento y mantener la comunicación con el paciente. El paciente debe visitar al médico a las dos semanas luego de empezar el tratamiento y luego al mes. También ayuda hablar por teléfono con el paciente para monitoreo de la terapia y para darle el sostén y apoyo requerido. La ayuda del médico es fundamental para ayudar al paciente a dejar de fumar.

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Estudios Originales:

Attitudes Toward Euthanasia, Assisted Suicide and Termination of Life-Sustaining Treatment of Puerto Rican Medical Students, Medical Residents, and Faculty +

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*Yolanda Otero Igaravidez M.D. ****

Abstract:
Objective: *To elicit the opinion of Puerto Rican medical students, residents and internal medicine faculty as to the appropriateness of euthanasia and physician-assisted suicide and end-of-life management.*
Design: *Survey using a 16-item questionnaire answered within a two-month period in the fall of 1996.*
Setting: *Rounds or faculty meetings at teaching hospitals located in the north, south and southwest of the island of Puerto Rico.*
Participants: *There were 424 participants. The questionnaires of 279 medical students, 75 medical residents, and 35 internal medicine faculty members were analyzed. Thirty-five questionnaires, which were incomplete or answered by non-Puerto Rican participants, were excluded.*
Main Outcomes Measures: *Frequency of support of active euthanasia, physician-assisted suicide, withholding or withdrawing life-sustaining treatment with informed consent was determined. Whether it was ethical to prescribe full doses of drugs needed to alleviate pain, even if it would hasten death, or agree to limit or restrict resources for the terminally ill was also determined.*
Results: *Forty per cent of the students, 33% of the residents, and 20% of the faculty supported euthanasia. If physician-assisted suicide were legalized, 50 per cent of the students, 43 per cent of the residents and 45 percent of the faculty would not be opposed to it. Sixty-eight per cent of the students, 67 per cent of the residents and 88 per cent of the faculty would support withholding or withdrawing life-sustaining treatment for dying patients with informed consent. Seventy-nine per cent of residents, 80 per cent of the faculty but only 54 per cent of medical students would prescribe full doses of drugs needed to alleviate pain in dying patients even if they would hasten death. Thirty-six per cent of the residents and faculty would agree to limit the use of medical resources for the terminally ill but only sixteen per cent of medical students would do so.*
Conclusions: *The acceptance of euthanasia was inversely proportional to the clinical experience of the respondents: 40 per cent among students but only 20 per cent by the faculty. Withholding and withdrawing of life-sustaining treatment was most acceptable to the faculty (88 per cent) but it was also favored by most of the students and residents (68 and 67 per cent respectively). Eighty per cent of the faculty, 79 per cent of the residents, but only 50 per cent of the students considered that prescribing full doses of drugs to alleviate pain if they knew it would hasten death, was ethical. The medical profession should take notice of evolving concepts in end-of-life management.*

Living is not the good, but living well. The wise man lives as long as he should, not as long as he can.
Seneca

In the last twenty years, landmark court decisions have favored the rights of seriously-ill patients to withdraw or withhold life-sustaining treatments (1,2,3). A serious controversy exists, however, as to the appropriate role of physicians in helping patients through their final exit.

Opinions as to the appropriate functions of physicians in the treatment of the terminally ill are being obtained from various segments of the population all around the world, but the point of view of future North American physicians of a specific ethnic and cultural origin has not been elicited (4). The multicultural influences which impact physicians in training in the North American pluralistic society make difficult to sample the opinions of specific ethnic groups. We have taken advantage of the relative unicultural environment of the island of Puerto Rico to

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determine the attitudes of Puerto Rican medical students, house staff, and internal medicine faculty in three medical schools and their associated hospitals to three important issues: euthanasia, physician-assisted suicide and end of life management.

Subjects and Methods

Medical students, internal medicine residents, and attending physicians in three medical schools and their affiliated hospitals, answered a 16-item questionnaire published by the New Physician and AMSA in 1994 (5). The questionnaire was handed out and collected in teaching rounds and faculty meetings within a two-month period in the fall of 1996.

A total of four hundred and twenty-four questionnaires were completed, 389 were found suitable for analysis. Questionnaires of twenty-one students who did not identify themselves as Puerto Ricans were excluded in an attempt to provide a Puerto Rican vision concerning these issues. Also excluded were twelve questionnaires that lacked definition of gender and two questionnaires where the level of medical training was not stated.

Hospitals were located in Río Piedras, Bayamón, Ponce and San Germán, in the north, south and the southwest coast of the island of Puerto Rico. Subjects were asked whether in terminally-ill patients they: 1) would support euthanasia; 2) if it were legalized, would engage in or approve physician-assisted suicide; 3) would support withholding or withdrawing life-sustaining treatment for the dying patient with informed consent; 4) would consider ethical to prescribe full doses of drugs needed to alleviate pain, even if they knew it would hasten death; 5) would agree to limit or restrict certain resources for the terminally ill. They were also asked to describe their medical education in decisions concerning the end of life and some personal demographic data.

Results

The questionnaires of two hundred and seventy-nine medical students, 75 medical residents and 35 internal medicine faculty were analyzed. Forty per cent of the students, 33% of the residents, and 20% of the faculty supported euthanasia (Figure 1). Seventy-four per cent of faculty did not.

If it were legalized, 10 per cent of the students, 12% of the residents, and 6% of the faculty would be willing to directly engage in physician-assisted suicide (Figure 2). Fifty per cent of the students, 43% of the residents and 45% of the faculty, while not willing to engage, were not opposed to physician-assisted suicide; only 25% of the students, 35% of the residents and 45% of the faculty were opposed.

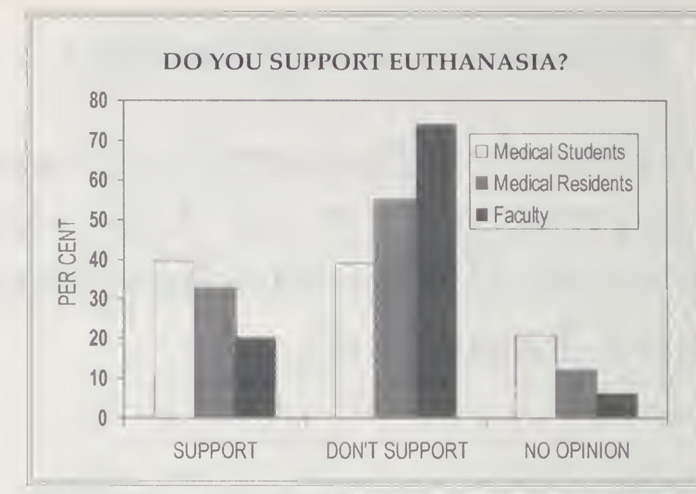


Figure 1. Euthanasia was most supported by medical students, followed by medical residents and faculty.

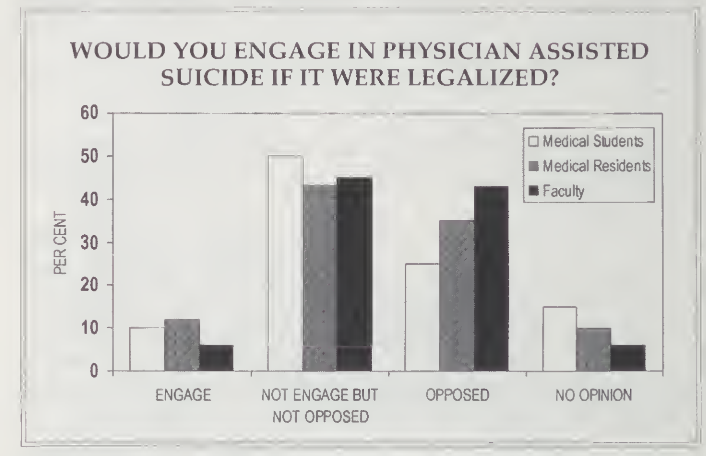


Figure 2. More than fifty per cent of the medical students, residents and faculty would engage or would not be opposed to physician-assisted suicide.

Most of the participants were willing to withhold or withdraw life-sustaining treatment. Sixty-eight per cent of the students, 67% of the residents, and 88% of the faculty would do so (Figure 3).

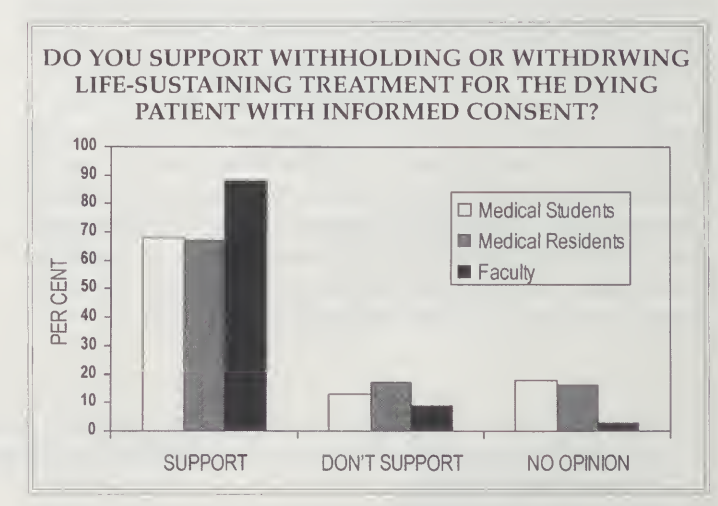


Figure 3. There was general support for withholding or withdrawing life-sustaining treatment in the dying patient, particularly from the faculty.

Fifty-four per cent of the students, 79% of the residents, and 80% of the faculty would agree to prescribe full doses of drugs to alleviate pain in dying patients even if they would hasten death. Nineteen per cent of the students would not agree to giving pain medication if it would hasten death. Surprisingly, twenty-one per cent of the residents and 20% of the faculty would either not use analgesics to relieve pain in terminally-ill patients or had no opinion on this subject (Figure 4).

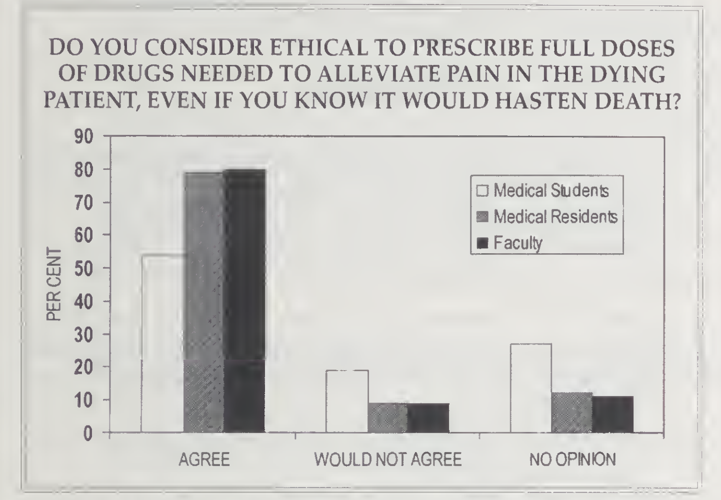


Figure 4. Fewer medical students than medical residents and faculty considered ethical to prescribe full doses of drugs to alleviate pain if it would hasten death.

Sixty-one per cent of the students, 44% of the residents, and 43% of the faculty would not limit medical resources for the terminally ill; 16% of the students, 33% of the residents and 43% of the faculty would; and 23% of the students, 23% of the residents, and 14% of the faculty had no opinion (Figure 5).

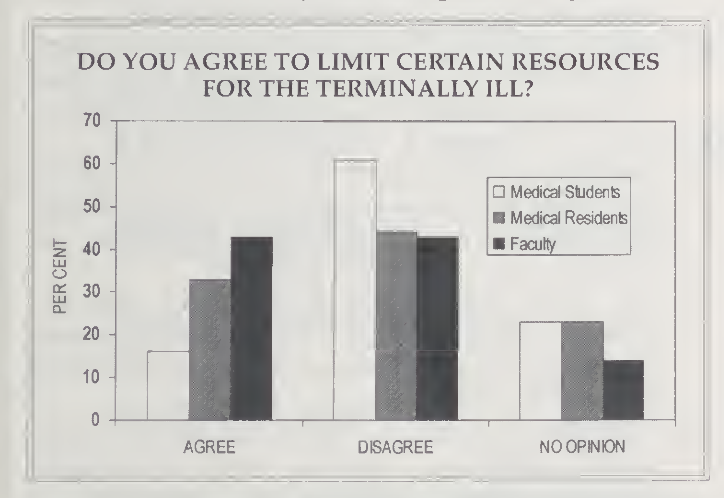


Figure 5. Particularly the medical students did not agree to limit resources for the terminally ill but the faculty was evenly divided.

Medical education concerning end-of-life decisions was considered inadequate by 54% of the faculty, 47% of the residents and 33% of second, third and fourth year students.

Comments

Despite the strong influence of traditional Judeo-Christian morality in our society, when life becomes an intolerable burden rather than a good, a growing secular view holds that helping people to die is a beneficent act. Proponents argue that in a democratic society of cultural, religious and moral pluralism, individuals should have moral authority over their own lives. In this view, the moral evil in murder is not taking someone's life but taking that life without consent.

This secular point of view, although present in varying degrees in the Western world, has been most clearly put into practice and articulated in the Netherlands. There, euthanasia and physician-assisted suicide are generally acceptable to the public and the medical profession (6,7). Criminal prosecution for these practices, although still technically possible, rarely occurs. In that small country of 15 million inhabitants, it is estimated that there are 9,700 yearly requests for euthanasia and physician-assisted suicide. And more than one third of these requests are carried out. The broadening of these practices, to those who are not terminally ill, is difficult to accept in other countries: In a case where a psychiatrist was taken to court for assisting the suicide of a 50-year old woman who wanted to die after the death of her two sons, the Dutch Supreme Court found that suffering, whatever its cause, may by itself justify physician-assisted suicide. It was the Court's opinion that the degree of suffering, not the cause, was the main issue (8,9).

It is increasingly apparent that requests for physician-assisted suicide are not unusual. Physicians are more willing to assist when pain and suffering due to physical symptoms are present. The majority of requests are not discussed among colleagues or evaluated adequately due to fear of legal prosecution (10). Nevertheless, many doctors have carried out euthanasia or physician-assisted suicide even though these practices are illegal. In a recent study, 22.7% of North American oncologists supported euthanasia and 45.5% physician-assisted suicide for patients with severe physical pain (11).

In our study, support of active euthanasia appeared to be inversely related to age and experience: mostly students, followed by residents, and then faculty favored it. Only 20% of the faculty would support the use of active euthanasia, while 40% of students did so.

Physician-assisted suicide was more acceptable than euthanasia. If it was legalized in Puerto Rico, more than half of our respondents would not object to physician-assisted suicide; but only 6% of the faculty, 12% of the residents, 10% of the students would engaged directly in such an activity. The willingness to engage directly in physician-assisted

suicide is much less than in Michigan in the spring of 1994 (12). It is also less than in the 1960 nationwide survey of specialty physicians in the master file of the American Medical Association (13).

When compared with students in Oregon, a State where physician-assisted suicide has been legalized, the point of view of Puerto Rican medical students appears very conservative (14,15). While in Oregon 55 per cent of the students "might be willing to write a lethal prescription" in Puerto Rico only 10 per cent of the students would be willing to engage in such a practice.

Although the principles of beneficence and respect for others would lead us to relieve pain at the risk of hastening death, some doubt persists, particularly in the minds of medical students, about its being ethical (15). Others fear the possible misinterpretations or legal consequences of effectively controlling pain with opiates if death is associated with it. It was surprising, nonetheless, that 21% of the medical residents and 20% of the faculty would not administer sufficient opiates to their patients to alleviate pain if this would hasten death.

There is no moral or legal controversy about withholding or withdrawing futile treatments at the request or with the consent of competent patients. Because there is no legislation on this subject in Puerto Rico, this is frequently avoided. Physicians in Puerto Rico, encouraged by legal counsel, try to avoid the issue of withdrawing life-sustaining treatments in dying patients. This may be the reason why 33% of the residents did not support or had no opinion about withholding or withdrawing such treatment.

The strictly Puerto Rican view obtained by this study shows that, although more conservative, our attitudes are not too dissimilar than those of other multicultural groups. The medical profession should take notice of our evolving concepts in end-of-life issues.

Resumen: *Por medio de un cuestionario, se obtuvo la opinión de 279 estudiantes de medicina puertorriqueños de tres escuelas de medicina, de 75 residentes de medicina y de 35 miembros de una facultad de medicina interna sobre decisiones que pueden considerarse en pacientes en fase terminal: Cuarenta por ciento de los estudiantes de medicina, 33 por ciento de los residentes y 20 por ciento de la facultad estaban de acuerdo con la eutanasia. Si ésta fuera legalizada, 10 por ciento de los estudiantes, 12 por ciento de los residentes y 6 por ciento de la facultad, participarían en un suicidio médico-asistido; aunque no dispuestos a participar, 50 por ciento de los estudiantes, 43 por ciento de los residentes y 45 por ciento de la facultad no se opondrían al suicidio médico-asistido. Sesenta y ocho por ciento de los estudiantes de medicina, 67 por ciento de los residentes, y 88 por ciento de la facultad estaban de acuerdo con retirar la terapia de sostén de pacientes moribundos con su consentimiento. Ochenta por ciento de la facultad y 79 por ciento de los residentes, pero sólo 50 por ciento de los estudiantes consideraron ético recetar la dosis de drogas requerida para aliviar el dolor en un paciente moribundo si esto podía acortar su vida. Sesenta y uno por ciento de los estudiantes de medicina, 44 por ciento de los residentes y 43 por ciento de la facultad no limitarían los recursos médicos disponibles para pacientes en fase terminal.*

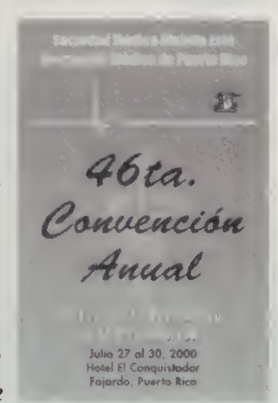
La profesión médica debe estar consciente de la evolución de la opinión de los médicos y los futuros médicos con relación al manejo de pacientes en la fase terminal.

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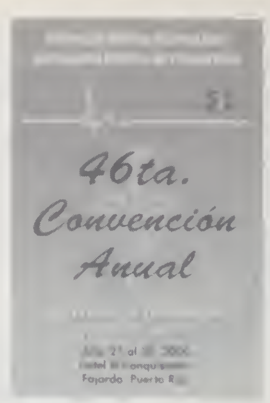
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Artículos de Revisión:

Suicide, Adolescents and Puerto Rico

Cornelius T. McQuillan, CSSp, MA, M.Div.; with collaboration of: José Rodríguez, Ph.D., MD***

Abstract: *Suicide is a multifactoral phenomena. This article reviews the recent literature and attempts to identify those factors which have particular relevance for Puerto Rican adolescents. Risk factors that correlate highly with the Puerto Rican experience include homosexuality, due to the hostility that the person may experience, depression, gender, prevalence of psychiatric disorders, lack of social integration and social skills, military experience, cultural and religious factors, alcoholism, substance abuse and unemployment/ poverty. The literature reviewed indicates that the Puerto Rican adolescent male is in a high risk group for suicide and that the risk increases with age, sexual preference, dysfunction in the family and substance abuse.*

Key Words: Adolescent Suicide, Risk Factors, Puerto Rico, Prevalence

The people of Puerto Rico, like many other cultures are impacted by many sociological, economical, political and religious factors as well as frequent natural disasters. Particularly relevant is the transition from an agrarian life style to a capitalistic industrial society. In 1940, 69% of the population lived in rural zones. Forty years later 67% were living in urban areas (1). Maldonado Denis (1963), describes the effects of this change to a rapid "...industrialization, with all its explosive implications for a traditional culture, has put this culture in check (en jaque), instigating a powerful dissolver of the traditional ways of acting and thinking in Puerto Rico" (2)(author's translation). The velocity of this change from a collectivistic to an individualist society has been particularly traumatic. Alvin Toffler's (1970), observations with regard to what he described as "Future Shock" seems an appropriate explanation of how unsettling this rapid change has been for this culture (3). Prior to the radical change from a well organized familial society whereby each member understood his/her particular role, bewildered parents find themselves in a state in which the children are more able to adapt themselves to an increasing more technological world. Torres-Zayas describes parents as feeling abandoned, misunderstood and not able to orient their own children (4).

Individualism as a value in Puerto Rico is somewhat different than in the United States. In Hispanic cultures it tends to manifest itself with respect to the internal unity of each person. Each individual attempts to preserve his integrity against the threat of being submerged in the routine of the external group. External norms are not given much importance, rather situations are valued based on feelings and emotions. De Roca quotes professor Cochran who describes this personalism as a preference not to sacrifice personal authority for the sake of the group nor family relations for the sake of relations with those outside the family (5).

Industrialization has brought about an internal migration to the urban centers which sorely lacked the substructures necessary for the rapid influx. Simultaneously, the political relation with the United states has provoked an external migration. Emigrants to the mainland confronted the same problems of other migrant groups such as racism. Today an equal number return to Puerto Rico. Those who return bring with them their "Newyorican" children. Some may be considered bicultural, but many neither identify fully with either culture. Many of these newyoricans feel like outsiders in Puerto Rico and many natives perceive the "newyoricans" as not identifying with Puerto Rico and its world view.

The North American invasion of Puerto Rico brought the public school system. This has led to greater escolarity, yet there is at present a 45% dropout rate at the secondary level. The school has replaced the mother as the central educator of her children. However, public schools provide a cognitive growth divorced from religious and moral education. Formally the mother was able to integrate faith and morales in the family's education. The Church was often remote, but served to validate the mother's educational efforts. Now, a generation or two later, parents attempt to educate their children while they themselves lack a solid or objective basis for teaching morality.

Along with citizenship came military obligations. More Puerto Ricans have died proportionally in American foreign wars than any other state in the Union and just as many numerically as the state of Mississippi. However, not all casualties result in death and Puerto Rican veterans have brought home their share of PTSD. Present unemployment level lead

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many today to see military service as an opportunity. Few realize the high rate of suicide among young men in the services (6).

Our era is characterized by a disintegration of our institutions. Some see the maxim of "divide and conquer" in the Americanization of Puerto Rico. All too often teachers attack the church by signaling its historical errors, but rarely, present an academically honest appraisal of its contributions. American protestant missionaries have literally divided the island into territories. Very few protestant churches have collaborated with the weak Catholic Church which served to unite the populace. They rather, perhaps unwittingly, help the American invasion by deepening the divisions. The proselytism of many of the sects has also provoked rampant skepticism toward the Church's moral teaching as well as a concomitant subjectivism. This has only served to acerbate the growing individualism.

According to Spaulding, who translated Durkheim's book on Suicide, there is a general agreement, based on various studies that the suicide rate is lowest for Catholics (7). It seems that the more individualistic religions have higher rates. It could relate to belief systems, but is more probably related to other emotional outlets provided through religious practices. There seems to be a correlation with social integration and religions which do foster socialization to varying degrees.

In an unpublished research project on religious affiliation and depression within three protestant denominations and Roman Catholics in Puerto Rico, Rodríguez (1998), found that protestants report more depressive symptoms in the Beck Depressive Inventory (8).

Meanwhile, the political status issue dominates all political questions and divides the society at all levels. However, the churches, politicians and teachers all agree that parents are to be held responsible for our present situation. Yet, our industrialized consumer society demands that both parents contribute to production. Thus children are raised in the streets with little or no supervision. This contrasts drastically with the agrarian past. Traditionally the father was the provider of the family who was the model of worker and lover of the soil. The mother had the ambivalent role of aligning herself with her children to protect them from the unquestioned authority of the father. However, she also aligned herself with her husband in order to better control the children (4).

In 1979 Torres-Zayas reported that 25% of women were working outside the home. This is of course much higher today. Parents are jealous about not sharing their authority with others. Authority over the children is the exclusive prerogative of the parents often not even shared with the grandparents. "The family is the primary unit in the sense of providing to its members the type of sympathies and mutual identification which makes possible the feeling of 'we'. The family provides the person his first and most complete experience of social unity" (4).

In the movement from the agrarian to an industrial society 'utility' has come to be one of its highest values. Families are smaller and each child is encouraged to develop his / her own talents and interests which provokes a growing emotional distance between members of the family (4).

Another factor greatly affecting the people of Puerto Rico is the widespread use of the means of social communication. Children are exposed to hours of unsupervised television. The media has a very strong influence in the socialization of the children, is often the source of incongruencies with the values of the family and in the case of American-made programs, with cultural values (1). Some "novelas" (soap operas) today would have been considered soft pornography to prior generations. Many today consider what is daily fare (mostly produced in the United States) on MTV to be hard core pornography! Is it any wonder that abortion is "big business" with nine clinics performing about 8,500 abortions annually. Marriages tend to be monogamous, but the divorce rate is about 50%.

The growing use of child care centers is another characteristic of today's society in Puerto Rico. More and more non family members have influence in the early development of children. Children are raised conscious that their parents are obliged to supply their needs, but are not reared with a sense of responsibility to also contribute to the well-being of the home (4).

Very often the father whose parenting time is often very short has a social life with a drinking group at the local neighborhood bar (9). The rate for alcoholism is one of the highest in the world. In 1984 Alba Nydia Rivera Ramos, a Social Psychology researcher, reported 500,000 persons affected by alcoholism (10). That was almost 15% of the population. This may provoke a transfer of the mother's affection from her husband to one of her sons. This can lead the father to feel alienated from the family system and displaced by his children. Both alcohol use and homosexuality have been correlated with suicide.

Meanwhile the wife may feel enslaved, exploited or deserted by her husband. "She talks about him a great deal, in contrast to his almost total silence concerning her" (4). Virility and "machismo" remain one of the dominant values inculcated in male children (5). While virginity is a dominant value inculcated in female children.

The Puerto Rican people have been described by Albizu Miranda and Marty as hospitable and gene-

rous, but in a study done in both Puerto Rico and Chicago feelings of hostility, lack of trust and a rejection of others has been indicated. The authors of this study conclude that "others" are only accepted superficially. This same study indicates strong feelings of insecurity and anxiety. These can be manifested by tendencies toward conformity, passivity and a relative lack of capacity to confront provocations from the environment and from social relations. This can be associated with exaggerated formalism of courtesy and good manners (11).

Pacheco and Lucca-Irizarry (1983) report that suicide is the second leading cause of death among university students (12). They compared UPI students with students enrolled at the State University of New York at Albany with regard to word associations. Interestingly, the stimulus word "accident" was more meaningful for the Puerto Rican group, followed by "death," while for the American group the most meaningful word was "death" followed by "time" and "suicide." The word "suicide" occurred in four associations for the Anglo group and in not one for the Puerto Rican group. Perhaps this is due to the more traditional religious culture in Puerto Rico.

Alba N. Rivera Ramos understands psychological problems to be related to economical issues. She reported in 1984 that 72% of the population was below the poverty level and only 34% were employed. 75% of mental problems treated in Puerto Rico that year were from low income families. Symptoms reported included anxiety, depression, low self-esteem, lack of goals or objectives, lack of incentives and suicidal tendencies. These symptoms correlate with unemployment (10). Today 2/3 of the population receive food stamps and the official unemployment rate which is known to be a very low estimate is at 24%. Both the lack of high school diploma and the unemployment rate can be very strong factors in teen's feelings of hopelessness and depression in Puerto Rico.

Parrilla (1987) found significant relationships in the scores on her "Escala de Identificación de Riesgo Suicida en Adolescentes" (IRSA - Scale of Risk Identification for Adolescent Suicide) between suicide attempters and a control group in a study done in Puerto Rico. The investigator found no significant difference between the attempters and the control group with regard to demographic differences such as age, grade and ordinal birth order. However, significant differences were detected between the items which compared family systems, experiencing humbling events, loss of a significant person, problems with interpersonal relations. Females scored significantly higher than males on the IRS. Breakups of romantic relation were also more common (8% higher) among the attempters than among the teens in the control group. Suicide attempters had 6% more humiliating experiences than those in the control group as well as a higher proportion having had the experience of the loss of a significant other or an object which held high emotional value. Parrilla also reports higher depression scores and more hopelessness (18% higher) and loneliness (26% higher) for the attempters than for the control group. The most significant difference was with regard to feelings of low self esteem with a difference of 58%. Finally this researcher found significant differences with regard to the concepts of life and death (13). She concludes the combination of low self worth, loneliness, hopelessness and guilt feelings to be crucial factors contributing to an overall state of depression.

Table 1
Adolescent Suicides in Puerto Rico

	Age 10-14	Age 15-19
1995	3	9
1994	1	14
1993	0	14
1992	1	12
1991	5	19
1990	1	9

A chart presented by Parrilla Cruz (1998) in the Monthly Circular: *Vida Saludable* (14).

She observes that in 1983 there were 14 suicides of teens between the ages of 10 and 19. It was then considered to be the third greatest cause of death in the age group of males and fifth for females. By 1985 it was listed as the fourth leading cause of death in Puerto Rico. There were 17 cases of teen suicide which was 6% of the 269 deaths. Males in that year were 67% of the cases with 18% of them between 10 and 14. Eighty two percent were between the ages of 15 and 19 and males in this group rose to 79% (13). Thus it can be seen that the risk was growing as a factor of age especially for the males.

In 1985 42% of all adolescent suicides came from homes where parents were divorced. Fifty seven percent were from homes where the father was unemployed. Nineteen percent of the victim's mothers had attempted suicide and 15% had an aunt who attempted or completed suicide. Thirty one percent had a history of mental illness in the family (13).

Of suicide ideators 42.59% were first born, 12.96% second born and 25.42% in the third ordinal position of birth order. Pills (73.80%) were the most common means of attempted suicide. Jumping was attempted by 14% of survivors. Parrilla calculates the critical age between the years of 15 and 17 (13).

Parrilla Cruz reports that by 1992 suicide had become the second most common cause of adolescent death in the USA and that between 5 and 8 attempters

were being treated in the emergency rooms of Río Piedras and Bayamón. She estimated that for each suicidal death there is between 150 and 300 others at high risk here in Puerto Rico (14).

In 1994, the last available statistics from the Department of Health in Puerto Rico, a total of 355 suicides were reported. Of this total 320 (90.14%) were males and 35 (9.86%) were females which seems to indicate that males in Puerto Rico are at higher risk. Of these 24 (6.7%) were teens between the ages of 10 and 20 years of age. Between the ages of 10 and 14, 5 males and no females committed suicide. Between the ages of 15 to 20 years of age 17 males and 2 females committed suicide. These statistics only include those that actually committed suicide and not attempters (15).

The Puerto Rican Department of Health also segregates these statistics into groupings according to the means used to commit suicide. A total of 2 teens, one of each sex, between the ages of 15 to 19 ingested either solids or liquids. A total of 12 teens hung themselves and of these 11 were males (three under the age of 15) while only 1 female over the age of 15 used this method. Fire arms were used by a total of 10 male teens of which 2 were under the age of fifteen (15).

In the report on violent deaths by age groups and Rates of the Department of Health of Puerto Rico for 1994, suicide is calculated at a 9.6% for all age groups. The rate for 10 to 14 year old is .1% and for 15 to 19 year old .6%. Seven (7%) for those between 10 to 24. While it climbs to 1.5% for those between the ages of 25 to 29 (15). Thus it would seem that like in the United States, the risk factor rises with increase in age. The same document reports a total of 1,313 deaths by accidents with another 173 of undetermined causes. Yet, it is often very difficult to ascertain the intention of the accident victim. How many of these so called accidents may have been intentional remains a speculative question, however the high numbers suggest that there may be far more than those which were recorded as suicides. The number of teens who died in accidents between the ages of 5 to 9 were 13 (.4%) with no suicides reported for this group. Between the ages of 10 to 14 the number of deaths by accident increases to 37 (1%) while those between the ages of 15 to 19 totaled 83 (2.4%). Suicides reported for these last two groups were 5 and 19 respectively and are consistent with what was already reported.

These reports from 1994 were obtained in February of 1998. One can only guess the reason(s) why more up-to-date statistics are not available from the Department of Health.

Table #2 is based on reports from the Puerto Rico Police Department. The manner of record keeping was changed between 1990 and 1991 making comparisons very difficult. Prior to 1991 ages between 10 and 19 are combined. After 1990 the statistics for each year is given and the sums according to sex are included, but not shown for each age group until 1996. However, statistics are segregated according to motives since 1990. Furthermore, with regard to teenagers, almost no information is available concerning motives with most cases recorded under unknown motives. Only one case is reported as due to family problems and another to personal problems.

Table #2

Teen Suicides in Puerto Rico According to Police Records from 1990

	Age:						
Year	**10-11**	**12-13**	**14-15**	**16-17**	**18-19**	**20-24**	**Totals**
1990					18*	62**	80
1991	1			3	4	15	23
1992		1	2	8	5	15	31
1993		1	2	5	8	24	40
1994	2	1	6	4	7	18	38
1995			5	5	8	24	42
1996			3	3	14	21	41
Totals	**3**	**3**	**18**	**28**	**64**	**179**	**295**

** include ages from 10-19 ** ages are from 20 -29*

In 1994 health records in Puerto Rico reported 24 teen suicides while the police reported a total of 38 (13). Even excluding the statistics from 1990 which does not specify the ages, the higher risk for suicide among older teens in Puerto Rico is clearly manifested. There is also significantly more males committing suicide in Puerto Rico. According to police less than 8% of suicides in Puerto Rico involve females.

Since 1995, the Police Reports on Suicide break down the statistics by both age and sex. Table #3 also demonstrates that teen males are at a 20% higher risk for suicide completion than teen females in Puerto Rico. Below graph #1 shows rather clearly this sharp difference. Table #4 breaks the statistics into age groupings and gender.

Table #3
Gender Differences Among Suicides in Puerto Rico According to Police Records

Year	**Male**	**Female**
1990	319	18
1991	240	10
1992	247	20
1993	272	25
1994	257	20
1995	239	26
1996	261	17
Totals	**1835**	**136**

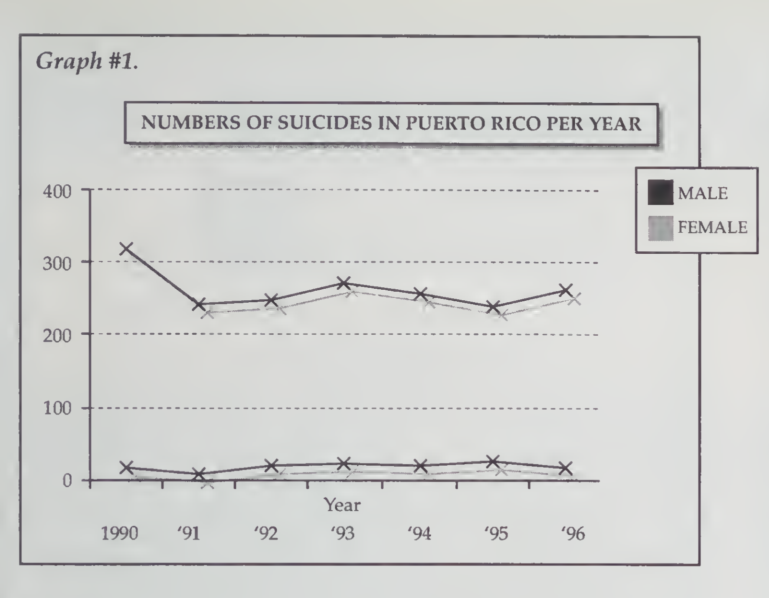


Table #4

Suicide Victims in Age Groups By Gender

Year	10-11	12-13	14-15	16-17	18-19	20-24
	Age Groups					
	M - F	M - F	M - F	M - F	M - F	M - F
1995	0 - 0	0 - 0	5 - 0	5 - 0	7 - 1	22 -2
1996	0 - 0	0 - 0	3 - 0	3 - 0	13 - 1	21 - 0

Total Teen Males: 79
Total Teen Females: 4

The alcoholism rate in Puerto Rico is one of the highest in the world and liquor is easily accessible to teens due to the proliferation of sidewalk bars. Rodríguez states that "Puerto Rico has more bars than schools and hospitals together" (7). Males have significantly higher rates of alcoholism in Puerto Rico than females. However, female use of alcohol is reported on the rise. The Isle of Enchantment is a machistic society where being a male is often equated with sexual prowess. Homosexuality is tolerated, but gays are deprecated, mocked publicly in the media and rejected in terms of their masculinity. The political relationship with the United States has been a double edged sword. No one can deny the enormous economic strides made over the last 50 years, but these rapid changes have caused many causalities and put the Puerto Rican family under much stress. The high unemployment rate with a 50% dropout rate from secondary schools added to epidemic drug abuse, unchecked consumerism, child abuse and domestic violence helps to create an environment of helplessness and depression. The high rate of HIV positive teens, the alarming rate of males diagnosed with hyperactive attention disorder the alarming rate of suicide among the elderly are further symptoms of a society in crisis (16).

Sánchez Lacay *et al.* did a study in 1982 of 41 adolescents at the Pediatric Hospital of the Medical Center in Puerto Rico, hospitalized due to attempted suicide. They were between the ages of 13 and 18. Eight percent (8%) of those admitted during that time were for attempted suicide. Sixty eight percent (68%) were females and thirty two percent (32%) were males. This contrasts with the statistics on the numbers of suicide fatalities in Puerto Rico, but may be due to the fact that adolescent males who attempt suicide use faster and more violent means than females. Males tend to use hanging, jumping from a high place as well as toxic medicines combined with alcohol. Females tend to use slower means where there exists greater opportunity for intervention. 66.6% used hanging (according to press reports from 1913 until 1981), toxic medicines (20%) and fire arms (13.3%) (17). Sixty eight (68%) percent of the subjects in this study had attempted suicide by means of ingesting medicines.

In general the subjects of this study had fallen behind in school. Forty-two percent (42%) reported problems in affect, twenty two percent (22%) had behavioral difficulties and twelve percent (12%) evidenced disturbed perceptions and thought patterns. Both males and females presented greater symptoms of problems related to affect and somatic complaints. Reasons given by the subjects were family problems (46%) especially with parents, wanting to die (31%), and problems with boy or girl friends (14%). Half the subjects live with only one parent; 42% come from homes of divorced parents and 18% from widowed parents. Over half of the parents were unemployed. Almost one quarter of the subjects had a relative that had attempted suicide and the majority had family members with affective disorder, drug use or other mental disorders. The most significant stressor noted was the number of attempts for the subjects which is consistent with the fact that females tend to attempt more often than males (17).

There is a foundation in Puerto Rico for the investigation and prevention of suicide. Table #5 shows the numbers of suicides for each year according to their statistics.

Table #5

Suicides in Puerto Rico by Age Groups
From the Foundation to Investigate and Prevent Suicide

Year	Total Teen Suicides	Age Groups 10-14	15-19
1990	12	3	9
1991	15	1	14
1992	14	0	14
1993	13	1	12
1994	24	5	19
1995	10	1	9

References: 1. Data on file. Pfizer Inc, New York, NY. 2. McLinn S, Williams D. High incidence of *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase) resistance in recent otitis media clinical trial isolates. Presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif. Abstract. 3. Hardy DJ, Hensey DM, Beyer JM, Vojtko C, McDonald EJ, Fernandes PB. Comparative in vitro activities of new 14-, 15-, and 16-membered macrolides. *Antimicrob Agents Chemother.* 1988;32:1710–1719 4. Retsema J, Girard A, Schelkly W, et al. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob Agents Chemother.* 1987,31 1939–1947. 5. McLinn S. Double blind and open label studies of azithromycin in the management of acute otitis media in children: a review. *Pediatr Infect Dis J* 1995;14.S62–S66 6. Khurana C, McLinn S, Block S, Pichichero M. Trial of azithromycin (AZ) vs Augmentin (AUG) for treatment of acute otitis media (AOM). Presented at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 4–7, 1994; Orlando, Fla. Abstract.

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BRIEF SUMMARY

INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia see **WARNINGS**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae* (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**)

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION.**)

NOTE: **Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).**

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy (For specific dosage recommendations, see **DOSAGE AND ADMINISTRATION**)

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX® Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin Therapy with ZITHROMAX® may be initiated before results of these tests are known, once the results become available, antimicrobial therapy should be adjusted accordingly

CONTRAINDICATIONS

ZITHROMAX® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy Although rare, fatalities have been reported (See **CONTRAINDICATIONS.**) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure** These patients required prolonged periods of observation and symptomatic treatment The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis"

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function.

There are no data regarding azithromycin usage in patients with renal impairment, thus, caution should be exercised when prescribing azithromycin in these patients

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes*, in individuals with prolonged QT intervals

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for Patients: Patients should be cautioned to take ZITHROMAX® suspension at least one hour prior to a meal or at least two hours after a meal This medication should not be taken with food

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur

Drug Interactions: Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Azithromycin did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects

The following drug interactions have not been reported in clinical trials with azithromycin, however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction Nonetheless, they have been observed with macrolide products Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised

Digoxin–elevated digoxin levels
Ergotamine or dihydroergotamine–acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia
Triazolam–decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam
Drugs metabolized by the cytochrome P^{450} system–elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay No evidence of impaired fertility due to azithromycin was found

Pregnancy: Teratogenic Effects Pregnancy Category B Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i e , 200 mg/kg/day) These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg In the animal studies, no evidence of harm to the fetus due to azithromycin was found There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed

Nursing Mothers: It is not known whether azithromycin is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman

Pediatric Use: (INDICATIONS AND USAGE.)

Acute Otitis Media (dosage regimen 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5) Safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established

Community-Acquired Pneumonia (dosage regimen 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5) Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults

Pharyngitis/Tonsillitis (dosage regimen 12 mg/kg on Days 1-5) Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established

Studies evaluating the use of repeated courses of therapy have not been conducted.

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug Approximately 0 7% of the patients (adults and children) from the multiple-dose clinical trials discontinued ZITHROMAX® (azithromycin) therapy because of treatment-related side effects Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e g , nausea, vomiting, diarrhea, or abdominal pain Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely

Clinical: Adults: *Multiple-dose regimen* Overall, the most common side effects in adult patients receiving a multiple-dose regimen of ZITHROMAX® were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported

No other side effects occurred in patients on the multiple-dose regimen of ZITHROMAX® with a frequency greater than 1% Side effects that occurred with a frequency of 1% or less included the following

Cardiovascular: Palpitations, chest pain
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice
Genitourinary: Monilia, vaginitis, and nephritis
Nervous System: Dizziness, headache, vertigo, and somnolence
General: Fatigue
Allergic: Rash, photosensitivity, and angioedema

Single 1-gram dose regimen Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX® were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple dose regimen

Side effects that occurred in patients on the single one gram dosing regimen of ZITHROMAX® with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%)

Single 2-gram dose regimen Overall, the most common side effects in patients receiving a single 2 gram dose of ZITHROMAX® were related to the gastrointestinal system Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%) The majority of these complaints were mild in nature

Children: *Multiple-dose regimens* The types of side effects in children were comparable to those seen in adults, with different incidence rates for the two dosage regimens recommended in children

Acute Otitis Media For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%)

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (5 8%), abdominal pain, vomiting, and nausea (1.9% each), and rash (1 6%)

Pharyngitis/tonsillitis For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%), and headache (1%)

With either treatment regimen, no other side effects occurred in children treated with ZITHROMAX® with a frequency of greater than 1% Side effects that occurred with a frequency of 1% or less included the following

Cardiovascular: Chest pain
Gastrointestinal: Dyspepsia, constipation, anorexia, flatulence, and gastritis
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, insomnia
General: Fever, fatigue, malaise
Allergic: Rash
Skin and Appendages: Pruritus, urticaria
Special Senses Conjunctivitis

Post-Marketing Experience: Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include

Allergic: Arthralgia, edema, urticaria.
Cardiovascular: Arrhythmias including ventricular tachycardia
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration.
General: Asthenia, paresthesia
Genitourinary: Interstitial nephritis and acute renal failure
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice.
Nervous System: Convulsions
Skin/Appendages: Rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis
Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste disturbances

Laboratory Abnormalities: Adults: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows with an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT), with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate

When follow-up was provided, changes in laboratory tests appeared to be reversible

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality

Children: Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Acute Otitis Media and Community-Acquired Pneumonia: The recommended dose of ZITHROMAX® for oral suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day)

Pharyngitis/Tonsillitis: The recommended dose for children with pharyngitis/tonsillitis is 12 mg/kg once a day for 5 days (not to exceed 500 mg/day)

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.
ZITHROMAX® for oral suspension should not be taken with food.

More detailed professional information available on request
Revised January 1997

ZC178A97

Pfizer U.S. Pharmaceuticals

"Su niño tiene otra infección bacteriana de oídos. Puede que necesite un antibiótico...y recuerde, tiene que tomárselo todo".

O pregunte a su médico sobre Zithromax.® Cinco días y ya.



Si el médico le receta un antibiótico para la infección bacteriana de oídos de su niño (otitis media aguda), pregúntele si Zithromax es adecuado para él/ella.

El UNICO ANTIBIOTICO PARA TOMAR UNA VEZ AL DIA POR CINCO DIAS.

A diferencia de otros antibióticos, Zithromax se administra solamente una vez al día por cinco días. Y cinco días son tan efectivos como la terapia convencional de diez días porque el efecto de Zithromax continúa por varios días después de la última dosis.

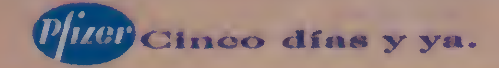
Zithromax tiene un agradable sabor a cereza que a los niños les gusta y se tolera bien. Los efectos secundarios más comunes son diarrea (2%), dolor abdominal (2%), vómitos (1%) y náusea (1%). Aunque las reacciones alérgicas son poco frecuentes, de ocurrir, descontinúe el uso de este medicamento y consulte con su profesional de la salud. Para detalles completos, véase un breve resumen en la próxima página.

PREGUNTE A SU MEDICO SI ZITHROMAX ES ADECUADO PARA SU NIÑO.

Para mayor información sobre Zithromax y un folleto gratis sobre el desarrollo del lenguaje y la audición,

llame al 1-800-587-DAYS.
O visítenos en www.KidsEars.com





The Foundation publishes a newsletter, "Panas Preset Vida" with information on suicide, appeals for support and resources for further investigations. It also provides conferences, help in crisis and a library as well as publish informative brochures and leaflets.

Krug *et al*. (1998) did a study that was recently reported in the New England Journal of Medicine on the correlation between suicide rates and natural disasters. They found a 13.8% in increase in suicide rates four years after floods. They also show a 62.9% increase in suicide rates in year following an earthquake (18).

These researches insist on the need for mental health support for the victims of these disasters and make the point that their studies show that the sequelae can persist up to five years after the disaster. The sequelae include PTSD, depression, insomnia, anxiety, substance abuse and domestic violence. They point out that there is not only the traumas caused directly by the natural disaster, but the tensions involved in acquiring governmental assistance, obtaining housing or waiting for insurance companies to reimburse losses. Unfortunately, Alaska and US Territories were excluded from this study. Yet an increase of 18.9 percent was calculated in areas affected by hurricanes, while other areas in the States only increased by .1%. This rate remained elevated for two years and then returned to country-wide levels. In areas that suffered flooding the increase was 13.8 percent while the rate was stable in all other states (18).

Differences were found based on sex and age, but these differences did not reach statistical significance. They report that younger men and older women where most severely affected. The increase for men was 21.8% and 14.5% for women. There was a 24.9% increase for those between the ages of 10 and 29 (18).

In their discussion of the findings they signal the association between mental health problems, depression and hopelessness, known risk factors for suicide and natural disasters (18). They explain the longer reaction times to floods based on the fact that floods do more damage and are more costly. Flood victims are more likely to make loans which increase stress over time.

McIntosh *et al*. (1994) found that the rate of suicides in Puerto Rico (7.7%) is somewhat lower than in the United States (20.4%) (19). Their findings based on the World Health Organization (WHO) statistics of 1991 report on the statistics for 1989. Puerto Rico shows a moderate rate compared to other countries. However, the discrepancies between Police and Department of Health reports are indicative that these statistics are not reliable and probably underestimate actual figures.

Suárez Cordero (1997), writes on the relationship between self-esteem and suicidal behavior. As a social psychologist he points out the factors in Puerto Rico that reduce the self-esteem of adolescents. She states that of 18,000 weddings yearly, 8,500 terminate in divorce, but 80% of these divorced parents remarry. For Suárez Cordero, it is the stress factors provoked by these rapid changes that affects the integral development of adolescents (20). Furthermore, the stressors from the environment with a high rate of school desertion, addictive behavior, the crisis in the values system, the open communication systems, high rates of domestic violence, sexual abuse of minors (21), criminal violence, unemployment, rampant consumerism and the idleness of many are said to impact the quality of life in Puerto Rico.

Self-esteem is intimately related with the self-concept. How we perceive others to value us helps us to learn to value ourselves. "Unfortunately in many cases youth receive messages of disapproval, lack of support, conditioned affect, humiliating experiences, lack of achievements, dependency, obstacles, lack of skills and no opening for participation" (author's translation) (20). This reality for many of the youth of Puerto Rico can easily lead to depression and suicidal thinking but can also be compounded by the identity crisis which is already so much a part of adolescent experience.

Conclusion

This review of the literature indicates that there is no one cause that can be identified as an explanation for suicide among teenagers. It seems that there are multiple factors which can mediate such an outcome. While there could be biological factors, they must be very minor, because they can't explain the vast differences between the number of males and females attempting suicide. Besides, the contagion theory (22), or imitation, is sufficient to explain the fact that some families manifest clear patterns of suicide.

Family systems theory maintains that some families dysfunctions in either their structures or in their communication skills are powerfully predisposing. This implies that members of these families have been deprived of a forum within which to learn both socialization and coping skills necessary to process their normal problems of living. As children develop, their problems become more complex, intense and requiring more and more skills, therefore these individuals are less and less prepared to cope. As young mature, they have greater accessibility to substances such as alcohol and drugs. Due to their lack of experience in the area of communication within the family, their social skills in other scenarios would probably be handicapped as well. This can lead to feelings of low self esteem, social inadequacy and isolation. The

family pattern reproduces itself leading to a breakdown of relationships. This can lead to depression or the intensification of depressive states already active within the individual. Some of the studies identify the relation between feelings of helplessness or panic and suicide. Possibly the idea that the pain, or frustration, of a lost relationship never ending scares some youth into a drastic attempt to end these feelings. Many suicidal teens have a history of running away.

It is possible that inappropriate cognition or irrational thoughts may be predisposing factors. The idea that the pain or painful isolation will never end is typical of teen thinking. Or the thought that no one could ever love them (relating to past failures, the crisis of sexual identity or conduct problems, etc.). Not having experienced unconditional love from significant others must relate.

The use of alcohol/substances seems to multiply the risk factors. It lowers inhibitions, distorts the perception of reality or can produce a myopic view of the situation. Alcohol has long been recognized as a depressant and the combination of depression and heavy drinking when combined with other factors may bring some individuals too close to the edge.

The phenomena of suicide can be compared to a stick of dynamite. Dynamite is a stick of gun powder, and a fuse which needs to be ignited. The powder is explosive and may relate to all the factors that are within the individual. They could be inadequate or inappropriate cognition, feelings of worthlessness, or helplessness, low self esteem, lack of social or coping skills, depression or other psychological disorders, etc. The fuse would be the factors from the environment. A history of failures, rejection, inabilities, frustrations, internalizing self-hate in the case of gays or lesbians, or the fear of being found out, alcohol or drug addition. The spark would be the event that ignites the fuse. It could be a failed exam, a lost relationship, a death of a significant other, any situation that could lead that particular person into a state of panic or severe anxiety. In the case of a homosexual it may be a sexual experience, or being identified as a gay. The spark can be any situation which would be considered difficult to most, but for the individual youth whose self concept is already vulnerable and without the skills for sharing and processing intimate feelings, such an event combined with alcohol, may lead to suicide ideation, and with a faulty cognition like "I can't stop thinking that it is the only thing that I can do" can prevent a teen from seeing any other way.

Suicide, in spite of all that has been written is confounding. We might be able to understand and analyze the factors that contribute to this phenomena, but it still remains very much a mystery. The statistics for Puerto Rico, although not sufficiently up to date, seem to be very much in line with the trend in the United States. Any psychologist working with youth can therefore expect to have contact with young people who are considering the possibility of ending their own life. I would conclude from this study, that an attempt to explore for suicidal ideation in the young should be a priority within evaluations. Counselors should make every effort to instill hope in their clients and offer them an effective means of communication during crisis.

Every school should have a counselor on the staff who has been made aware of the proportions of suicide attempts by teens. These counselors should organize prevention programs for all students especially since the literature shows that most students know a peer who has attempted. Contagion has been shown to be a factor, so institutions must prepare themselves, in the eventuality of a suicide attempt, to adequately address the issue. Special help should be available to youth with sexual identity problems. For example, in New York City students have the options of a special school for homosexuals. Teens need programs to strengthen their feelings of self worth and to develop their social skills.

Teachers too should be given workshops and trained to recognize the signs of depression and be able to make referrals to school counselors. They must be made aware how sensitive some teens are to school's pressures. Schools should also make available discussion groups or growth (therapy) groups where students can meet to learn the communications and problem-solving skills that they may not have learned at home. Churches too could do preventive work by addressing the topic in youth groups and making teens more aware of alternatives. Religious leaders must become more sensitive to the vulnerability of youth with identity problems and clearly communicate to them a message of hope rather than condemnation. Graduate programs in psychology could prepare students to be available to the larger community in "reach out" projects giving presentations in the communities and to schools, groups and in the "residenciales" (public housing projects). The military services must address more adequately the issues of homosexuality and alcohol dependence.

At a legislative level, the local congress should be made aware of the correlation between teen suicide and alcohol consumption. We cannot be so naive to think that a law will resolve the problem, but allowing minors to have easy access to liquor makes little sense either. The work of King *et al.*, which demonstrates the influence of the media, and its support of the contagion theory (22) should be brought to their attention. Again, not with the aim of enacting legislation, but as a way to raise the level of consciousness within the media to present more realistic accounts of the

negative consequences of suicide and suicide attempts on the lives of both the victim and their families and friends.

The Puerto Rican culture is in crisis and our youth is very vulnerable to its tensions and conflicts. A head-in-the-sand approach will not make the problem disappear. Suicide is a complex issue, requiring a complex multilevel and multi-faceted response. Therefore it must be met at therapeutic, legal, education, religious and social contexts.

Abstracto: *El suicidio es un fenómeno multifactorial. Este artículo repasa la literatura reciente e intenta identificar aquellos factores que son particularmente relevantes para los adolescentes de Puerto Rico. Los factores de riesgo que tienen una correlación alta con el fenómeno en Puerto Rico incluyen la homosexualidad por la hostilidad presentada hacia el sujeto, la depresión, el género, la prevelencia de desórdenes siquiátricos, la falta de integración social y destrezas sociales, la experiencia militar, los factores culturales y religiosos, alcoholismo, abuso de substancias y el desempleo/pobreza. La literatura revisada indica que el varón puertorriqueño está en un grupo de alto riesgo de suicidio y que el riesgo aumenta con la edad, la preferencia sexual, las disfunciones familiares y el abuso de substancias.*

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Artículos de Revisión:

Adolescent Suicide: A Review of the Literature

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*with the collaboration of: José Rodríguez, Ph.D., MD***

Abstract: *This article reviews the literature on the risk factors related to teen suicide in the United States and Puerto Rico. Findings indicate the interplay of multifactors including depression, homosexuality—due to the hostility that is often experienced by the person—, sexual abuse, lack of coping, social and problem-solving skills stemming from family dysfunction, feelings of isolation and helplessness, contagion, gender differences, alcohol and drug abuse, psychiatric disorders, biological factors, as well as natural disasters. Included in this report are some statistics on the prevalence of suicide among teens and in the military.*

Key Words: Teen suicide, Risk factors, Prevalence

Introduction

Suicide, committed by any person at any age is a tragic event. One is disturbed to learn that about half of those who commit suicide had seen a health care professional within approximately a month before choosing to end their lives (1). Nevertheless, this phenomena has been neglected as an important one perhaps due to the negative stigma which it projects. Six children commit suicide every day in the United States (2). 300 to 375 suicides are committed each year for the last 10 years in Puerto Rico (3). There is an enormous quantity of literature on the topic; unfortunately, there is far too little to be found with regard to studies done in Puerto Rico.

Definitions

Emile Durkheim (1966) has defined suicide as a "death which is the direct or indirect result of a positive or negative act accomplished by the victim himself" (4). Other terms that are found frequently in the literature included completed suicide which Davis and Sandoval define as "a death caused by the initiation of a deliberate set of actions leading to loss of life." This term is often contrasted with attempted suicide defined as "behavior directed against oneself that leads to self-harm or is considered by the adolescent (or evaluator) to have had a strong potential for self-harm." Finally, one frequently comes across the term suicidal ideation which refers to the serious thoughts in which a person considered the option of ending their life. (5) Studies often use these distinctions in their analysis of data.

Prevalence

In January of 1996 the American Association of Suicidology reported that each year more than 4,000 US teens take their own lives. This organization estimates that for every completed suicide there were approximately 20 attempted suicides and that suicide is the third leading cause of death (with an 11% rate) for teens, following accidents at a 36% rate and homicide at a 17% rate. (6)

McIntosh *et al.* (1994) report that while youths between the ages of 15 and 24 years of age represented 14.7% of the population in 1989, they made up 16.1% of the suicides (2). Thus, teen suicide rates are higher than the number one would expect proportionally and they are the second highest risk group.

A study of a peer-listening phone service indicates that mid adolescents (14-16) were more likely to call regarding suicide, abuse, sexuality and pregnancy (7). Interestingly, calls regarding suicide, abuse and death were more likely to occur in the winter and spring. Both winter and spring are exam and grading periods which may be related to stress and anxiety in teens. Spring is also a time for a return to outdoor activities and the use of sporty clothing. Many teens may be overly concerned with body image and not fitting the "ideal" sexual icon.

Ciske and Edwards (1997) claim that over 100,000 suicide attempts were made last year in the United States. Of these, they claim that 30,000 were by gay and lesbian youths between the ages of 15 and 23. Furthermore, they maintain that the gay population is only about 10% of the teen population, but that they commit 30% of the suicides. The frequency of lesbian suicide is double that of their peers while the frequency of male suicide is 6 times greater than that of heterosexuals (8). They suggest that gays are at a

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higher risk for substance abuse, school dropout and chronic depression which are associated with suicide in adolescents. In Puerto Rico, there exists a lack of research in this area.

McDonald Culp *et al.* (1995) state that suicide is the third leading cause of death for 15 to 24 year olds. They did a study on depression in teens using 220 students between the 6th and 12th grades in two Midwest parochial schools. Sixty percent of the middle school students and 57% of the high school students had scores on the Center for Epidemiological Studies Depression Scale (CES-D) of 16 and above (which indicates depressive symptomatology). Six percent reported having attempted suicide. Problems experienced by students were: loneliness, 66%; academic, 64%; not feeling good about yourself, 55%; depression, 54%; and problems with friends, 50% (9). Eleven percent of the students admitted to drug use twice a month and 39% were using alcohol bimonthly. Thirty percent of the students reported suicide attempts or thoughts. Twelve students or 6% had made an attempt whereas 11% indicated that a friend had attempted suicide. Of these 12 attempters, all had CES-D scores above 19. The authors conclude a correlation between depression and isolation for those at high risk.

The National Mental Health Association reports in their pamphlet on Suicide -Teen Suicide, that almost 5,000 teens, between the ages of 15 and 24, take their own lives. They also report that the rate has tripled since 1960. In this same organization's Suicide - General Information, they state that there is an estimated ratio of 10 to 1 between attempts and suicide. Furthermore they report that between 30 and 40 percent of suicide victims have made previous attempts and that a person that has attempted suicide is at 100 times greater risk during the first year after an attempt. Young people make up 20% of male and 14% of female suicide victims and is one of the leading causes of hospital admissions in people under 35. One third of suicide attempts are by persons diagnosed as suffering schizophrenia (10).

Military and Suicide

Within the military of the United States, between the years of 1980 and 1993 suicide accounted for 13% of all deaths of males and 12% of women. The number has remained fairly constant with approximately 245 deaths per year, but the rate has increased about 25% (11.9 per 100.000 in 1980 to 15.0 in 1993). Of those that committed suicide 48% were younger than 25 years of age. 95% of these are males who commit suicide at a rate almost 3 times the rate of females. The Marine Corps had the highest of all fatality rates of all branches with a 14% suicide rate. The Navy's suicide rate was the lowest (11.0) of the services according to the National Mortality Profile (11).

One fourth of all Air Force deaths between 1990 and 1995 were suicides. This translates into one suicide every six days. Thirty two percent of Air Force suicides were tied to substance abuse - alcohol. Financial problems were found as a source of stress and conflict in about 25% of these cases. Lost relationships and the consequent depressions were related to 60% of Air Force suicides. The remaining 40% were associated with work stress. This statistics do no include single car accidents. The group seen as highest in risk consists of those between the ages of 25 and 29 who have marital problems. Many may lack coping, social and communication skills (12). Due to the 24% unofficial unemployment rate, many Puerto Ricans opt for Military Service which puts them into a higher risk group.

Risk Factors
Homosexuality

Savin-Williams (1994) reports that gay male and bisexual youths are disproportionately at risk for stressors that may lead to suicide (13). They often feel isolated from their peers, family, and religious, social and educational institutions. They have a perceived need to keep their sexuality a secret and experience chronic stress in relation to "coming out" or having their orientation discovered. Many have experienced rejection, mistreatment or have become the focus of family dysfunction. This author reports that 40% have experienced violent attacks, that 61% of these occurred in the family and twenty two (22%) percent had been abused sexually. Studies have indicated school-related problems, including 40% truancy, 28% dropout and 60% having failed a grade. This investigator maintains that 6% of runaways have identified themselves as homosexual. However, all these statistics tend to be very low due to the fact that most teens have not established a clear understanding of their sexual preferences and due to social pressures are not likely to admit to homosexuality (13).

Savin-Williams claims that suicide is the leading cause of death among lesbians, gay male and bisexual youths. He maintains that they constitute 30% of all adolescent suicides. He reports that suicide attempts by this group are often associated with "sexual milestones." These include "coming out" or coming to identify oneself as gay. Eighty five percent reported using drugs and were determined to have come from dysfunctional families. At the time of their first attempt they reported feeling hopeless, worthless, alienated, lonely and helpless. When this group was compared with gay youths who did not attempt suicide they were found to have come to an awareness of their gay feelings at a much earlier age. Also reported are psychiatrist's opinions that the most frequent causes of adolescent gay suicide are feelings of disenfranchisement, social isolation, rejection from family or peers and self revulsion (13).

Remafedi (1987) found that the younger the teen came to terms with his homosexuality the higher the risk for psychological problems. Of his sample of 29 gay and bisexual youths 72% had been treated by mental health professionals. Five of nine who where hospitalized had attempted suicide. All but one of the sample had contemplated suicide at one time or another. Ten subjects (34%) of the sample had attempted suicide and two on multiple occasions (14).

Nelson (1994) has criticized the special issue on adolescence of the American Psychologist for having manifested significant heterosexist bias. This author affirms that gay and lesbian youth are at a three times greater incidence of suicide. He also indicates that one study has found that between 25% and 40% of homeless adolescents are self-identified as homosexuals. He observes that the issue failed to include sexual minority groups. Substance abuse is also cited as being three times higher among this population, as well as problems of social stigmatization, isolation and the internalization of this social hatred (15).

Schneider *et al.* (1991) compare gay and bisexual suicide ideators with regards to their HIV status. This study focused on the biological risk of developing AIDS and AIDS-related life events. Both were found to predict suicide-related outcomes. Their findings indicate that in HIV- subject's past depressive symptoms and loneliness alone predict suicide intent. This study indicates a substantial level of suicidal ideation among gay and bisexual men at risk for AIDS, regardless of HIV serostatus. Past levels of psychosocial functions is more predictive of suicide intent among HIV+ compared with HIV-suicide ideators. Events predict suicide intent more powerfully than current distress in subjects. The authors suggest that suicide ideation may be a way of coping (16).

Depression

Depression affects about 17.6 million Americans yearly. Between two (2%) and five (5%) percent of these are children with as high as ten (10%) percent in the clinical population (17). Studies indicate that depression is associated with the majority of suicides which is ranked as the eighth cause of death and third for those between the ages of 15 and 24 years of age. The DSM-IV reports a high mortality for those who suffer depression with as many as 15% committing suicide (18). There is no gender differences reported for depression of children between the ages of six (6) and twelve (12) (17). However, among pubescent teens the prevalence for females is double that of males. One of the characteristics the DSM-IV uses to determine a diagnosis of depression is the presence of suicide ideas as well as thoughts about dying which are not simply fears about death, but indicate an obsession with death (18).

In one of the latest editions of the American Psychologist, Dante Cicchetti and Sheree Toth (1998) have written on the correlation between depression in children and adolescents and early development. They also attest to a strong association between depression and adolescent suicide (19). Their studies lead them to conclude a prevalence of major depression of between .4 and 2.5% for children and between .4 and 8.3% for adolescents. The prevalence for an experience of major depression during adolescence is calculated at between 15 and 20% (19).

Cicchetti y Toth maintain that individuals adapt in a functional way the organization of cognitive, socio-emotional, representational and biological dominions. However, depressed individuals have incoherent and pathological organization in their systems which these authors call depressotypic organization (19). Noteworthy is the higher incidence of depression among children of depressed parents, especially mothers. Investigations indicate different lobule arousal in depressed children. Apparently depressed mothers' responses to their babies are less adequate and results in not only the child learning not to trust others to provide for their needs, but even physiological changes in brain activity related to attraction and avoidance behaviors. Children of depressed mothers tend to avoid others and therefore fail to learn other socialization skills at later developmental stages. Isolation of these individuals can also affect their learning of coping and problem-solving skills. It is believed that not having developed healthy attachment to their mother they do not learn the social skills necessary to relate with others.

Panic Disorders also interrelate with suicide and depression. Perhaps the lack of social skills, feelings of rejection and isolation, when combined with a panic attack, leave the individual with no resources or support system to help them cope with the extremely intense feelings of helplessness and impending doom.

Estimates for Puerto Rico indicate a six (5.9%) percent prevalence of depression among adolescents between the ages of four (4) to sixteen (16). However, the problem of co-morbidity with opposition and attention deficit disorder are probably masking higher rates (20).

Sexual Abuse

Suicide has been recognized as one of the *secuelas* of childhood sexual abuse. Finkelhor and his associates described a national poll, conducted in July of 1985 by the Los Angeles Times, which surveyed 2,626 men and women by telephone. Results disclosed that 27% of women and 16% of men had some experience of sexual abuse (21). A study done in 1995 on 236 college women found that 26% had experienced moderate

adolescent victimization and 33% severe. Furthermore, as children 47% had been victimized moderately and 12% had experienced severe childhood victimization (22). Collings found in a study done in 1994 that 9% of a group of 326 male social science students had reported contact sexual abuse. His study also showed that male sexual abuse is associated with later problems in psychological adjustment. Symptoms of depression, suicidal ideas and attempts, isolation, substance abuse, confused sexual identity are recognized as some of the *secuelas* associated with childhood sexual abuse (23). With such high occurrence it would seem that therapists must explore this possibility of childhood sexual abuse with any depressed individual or suicide attempter. Or in the case of known victims of childhood sexual abuse recognize such experience as a high risk factor for a possible suicide attempt.

Biological Factors

Malone (1996) confirms that suicide is the third leading cause of death among the 15 to 34 year olds. He maintains that suicide is a serious complication of Major Depressive Disorder. His studies indicate the possibility of an underlying serotonin dysfunction as related to the threshold for acting out suicide ideas. He has found lower serotonin metabolite levels in the spinal fluids and more blunted prolactin response to fenfluramine in those suicide victims who do most medical damage to themselves compared to those who do less medical damage. Malone continues that a Dr. Victoria Arango has identified alterations in serotonergic neuron projections to specific regions of the frontal cortex (the most sophisticated area of the brain and involved in the regulation of mood and impulsiveness. He calls for more research on the possible serotonin deficiency hypothesis of depression (24).

Ubiert Prats (1997) reports that postmortem studies of suicide victims reveal abnormalities based on examination of the serotonin neurotransmitter system. Low levels of serotonin may result in disinhibition or affective changes that could result in suicide. He states that lesions in the prefrontal cortex are associated with the development of depression, aggression and disinhibition. This author also maintains that the pharmacological treatment for depression acts directly on the serotonin system and reduce suicidal impulses (25).

Brent (1997) reports that there is greater concordance for suicide in identical twins compared to fraternal twins (26). This researcher states that Roy found psychiatric patients who had attempted suicide had higher rates of attempts in their relatives than non-attempters. Families of suicide victims have higher rates of attempts, depression and substance abuse. Recognizing the possibility of imitation, this author is more inclined to further genetic studies. That is because the evidence indicates that there is a greater concordance with biologic relatives than those adopted (26). However, he opts for the family system theory with regards to therapy. Brent states that members of families who have had a relative attempt suicide are at 4 times higher risk for suicide.

Contagion

The National Center for Injury Prevention and Control has published a report from a national workshop (27). They confirm the rate increase of suicide for persons between the ages of 15 - 24 to have climbed from 4.5 in 1950 to 13.5 per 100,000 in the nineties. A risk factor that seems particular to this group is suicide "contagion." They define suicide contagion to be a "process by which exposure to suicide or suicidal behavior of one or more person influences others to commit or attempt suicide" (28). They report that statistically significant excess suicides are seen with relation to nonfictional newspaper and television coverage of suicide. They also affirm the clustering as an effect of contagions which appears strongest among adolescents. It is not the reporting of a suicide that is of concern to this group, but how the media portrays the event. They are concerned that simplistic explanations or single factors not be presented, but rather the complex interaction of many factors as well as a psychosocial history. Prominent, excessive and repetitive coverage is seen as promoting contagion. Reporting can often focus too closely on the positive statements of those that knew the deceased, failing to mention his/her problems and difficulties.

Suicide contagion was studied in a psychiatric Hospital. This study was realized due to the phenomena of suicide contagion within communities and the statistical evidence which the authors affirm supports the clustering of adolescent suicides. Contagion was noted as occurring in small, close, well-established networks of friends. However, this study found no evidence of behavior clustering in an inpatient unit where acute care is given to adolescents.

Daniel Castellanos (1997) is in the early stages of analyzing the effects of television reports on suicide. "Copy cat" suicides are recognized because they closely imitate some programs which have included detailed descriptions of how to commit suicide. Features that are important include the details of the method used, whether the consequences are presented, the stressors, treatment and the characteristics of the adolescent who commits the suicide. He points out that many programs do not highlight or even mention the possible negative consequences such as disfigurement, paralysis or brain damage (29).

Phillips and Paight (1987) also studied the question of suicide contagion. They were not able to replicate earlier findings of Gould and Schaefer who studied

the effects of fictionalized accounts of suicide on the rate of suicide (30). The early study had been on subjects in the area of New York City. Gould and Schaefer's study was conducted in California and Pennsylvania. The New York Study was so statistically weak that when all three studies are combined, they fail to show a significant difference. However, these fictionalized accounts were only televised on one occasion where actual accounts of suicide are broadcast on several stations repeatedly which may account for the discrepancy between studies. In Puerto Rico, no study has been conducted on contagion and suicide.

Gender Differences

Reifman and Windle (1995) studied suicide behaviors as a function of depression, hopelessness, alcohol use and social support. They used two high school samples: one of 698 students and the other of 283. They report that suicide for 15 to 19 year olds has increased from 3.6 per 100,000 in 1960 to 11.3 per 100,000 in 1988 while the rate for the overall population only increased slightly (31). These authors calculate that for every seven deaths of those between the ages of 15 - 19 one is due to suicide. They look to three theories for explanation of this phenomena: Baumeister's escape theory, hopelessness theory of depression and the alcohol myopia theory. Baumesister's escape theory "posits that heightened awareness of one's own failures to meet personal and social standards, accompanied by intense negative affect and feelings of worthlessness, motivate the individual to avoid thinking about situations that carry negative implications about the self." Alcohol myopia is described as a result of consuming alcohol which restricts one's attention to only immediately salient stimuli. Thus, when considering risky behavior, inhibitory factors may be blocked from awareness while instigating factors may be intensified. Learned hopelessness is expressed by suicidal individuals who are not able to conceive of any other solution for their desperate or hopeless situation (31).

These researchers also point out gender differences. Males complete suicide more often than females, but females attempt suicide more often than males (31). This relates to the methods used. Males tend to use more violent and rapid means, guns, hanging themselves, etc. According to Parrilla Cruz, females tend to use less violent and slower means such as an overdose of drugs (32).

McIntosh reports that the male rate of suicide exceeds that of female suicides and that sex has the greatest predictive power (2).

Alcohol Use

"The recent hopelessness theory of depression sees hopelessness as a cause of a subtype of depression called 'hopelessness depression'" (31). The literature records mixed results. However, depression is indicated as a stronger predictor of future suicide. According to the theory of alcohol myopia, consuming alcohol restricts one's attention to only immediately salient stimuli. That is, alcohol myopia lowers inhibitors and the awareness of other factors that tend to inhibit risky behavior as well as intensify a single emotional state. These authors' investigations have led them to conclude that depression and alcohol consumption are independently and prospectively related to some or all suicidal behaviors. The structural design of their investigation strengthens the argument for presumed causal relations to suicidal behaviors (except completion) however, it does not rule out the possibility of other variable causations. It does eliminate the possibility of reverse causal process. Hopelessness did not predict later suicidal behaviors in this study. The hypothesis derived from the escape theory was not supported by this longitudinal analysis. However, family support was shown to be negatively related to suicidal behaviors cross-sectionally (31).

Gruenewald *et al.* (1995) have presented a very interesting study showing a correlation between alcohol sales and suicide rates. Alcohol is understood as a disinhibiter, but their study distinguishes between drinking beer, wine and spirits. Alcohol is also an indicator of social disintegration which is associated with suicide (33). These authors point out that other studies have shown that suicide is a function of age, gender, and race. The rate increases generally for age, is greater for males and less for non-whites. There is also the factor of economic opportunity. This study based on alcohol sales indicates a 1.5% increase for each 10% increase in spirits sales (not beer or wine). They were able to confirm that unemployment is positively related to suicide rates. Religiosity too is negatively related. Percentages drop in areas where Mormon or Southern Baptists populations are high. There was a 1.8% decline for each 10% increase. Previous studies had taken all liquor sales into account but findings were inconsistent due to comparative rarity of units and mis-specifications of controls. However, this study was very careful to distinguish between the consumption of spirits.

Psychiatric Disorders

Jan Fawcett, M.D. (1996), makes the distinction between short-term predictors and long-term predictors of suicide. This study indicates that a high level of anxiety was the most important short-term predictor of suicide. Fawcett states that panic attacks and anxiety which are manifested by worry, insomnia, anxious anticipation and diminished concentration as well as alcohol abuse predicted suicide over the short-term (34).

Shaffer *et al.* (1996) concluded in a study of psychologic autopsy on 170 children and adolescents that

committed suicide between 1984 and 1986 that most commonly a mood disorder alone—or in combination with conduct disorder and/or substance abuse—characterize suicides among teens (35). This study reveals that 90% of young people who committed suicide met criteria for at least one DSM III psychiatric diagnosis. Sixty-one percent met the criteria for mood disorder, 52% for major depressive disorder and 10% for adjustment disorder, 4% for bipolar disorder and 12% for depression otherwise not specified. All but five met criteria for conduct disorder and 27% for anxiety disorder. Seventy-one percent of the subjects committed suicide younger than 13 years of age. The prevalence of most psychiatric diagnoses increased with age. Gender differences showed that substance abuse and dysthymia occurred almost exclusively in males and major depression was twice as common in females (35). The authors conclude that reckless and runaway behavior remain a significant predictor of suicide risk for boys after controlling for mood disruptive and substance abuse disorders. Interestingly, 46 of the subjects had had contact with a mental health professional before their death. For males, a previous attempt and a diagnosis of a mood disorder and Substance Abuse or Alcohol significantly increased the risk of suicide. SAA was present in about two thirds of 18-19 year old males subjects who committed suicide. For females a previous attempt and a diagnosis of a mood disorder significantly increased the risk (35).

Levy *et al.* (1995) did a study on adolescents admitted to a general hospital emergency room. They found that the best predictor of suicidal intent was a sense of hopelessness. They tested 78 adolescent attempters between the ages of 12 and 18. 61 were females (80%), 75% were Caucasian, 12% Hispanic, 10% African-American and 3% Asian. 92% attempted suicide by drug overdose. This was a first attempt for 72% of the subjects.

Precipitating events were problems with parents (36%), and problems with boyfriends/girlfriends (25%). Levy *et al.* used the Hopelessness Scale for Children, took into account the social economical status (SES) and employed the Suicidal Ideation Questionnaire as well as the Model of Family Functioning. The suicide Intent Scale was also administered. Results showed that those who were admitted medically had more dysfunctional family scores. Hopelessness predicted both suicide intent and suicidal ideation. However is was not found to be a mediating variable. A regression analysis showed that family dysfunction predicts hopelessness and hopelessness predicted suicidal ideation (36). These authors concluded that hopelessness had the strongest effect in predicting both suicidal thoughts and attempts. Contrary to expectation, higher SES was seen as related to more serious suicidal intent (36).

There may be a correlation between suicide and anorexia or bulimia. According to an article published in the Boston Globe by Huebner (1997), the NIMH reports a 10% death rate with deaths attributed to starvation, cardiac arrest and suicide. According to the same article 90% of Americans affected are women and most of them are young. Anorexic people lack self esteem, have difficulty communicating their feelings, and those with bulimia often feel guilty and depressed (38). Between 40 and 80% of eating disorder patients suffer depression. Wang found that those with severe anorexia and bulimia have low levels of serotonin and norepinephrine which does not normalize with weight gain (38).

In an update on Dr. Shaffer's studies he corroborates earlier findings. The suicide rates in 1991 are the same as they were found to be in 1988 when they peaked. However over the past 15 years the suicide rate for boys has tripled (39). In 1990 firearms were used in two thirds of the teen suicides. The preferred method by the remaining males was hanging. This researcher points to a 90% rate for a psychiatric diagnosis of adolescent suicides. He refers to three studies which indicate some form of depressive disorders or alcohol/substance abuse especially for those over 17. Shaffer also observes the low levels of serotonin metabolites in victims blood. He accepts that contagion is still a controversial issue, but points to an important study done in Germany where a TV story presented a young man committing suicide by lying across railroad tracks. Both times that this story was aired it was followed by an increase in the suicide rate by that method.

Suicide and Coping Skills

In their article on Coping, Depression and Adolescent Suicide Attempts, Anthony Spirito *et al.* (1996) state "that maladaptive coping strategies have been viewed as either predisposing variables or precipitating factors not only in depression but also in suicidal behavior in adolescents" (40). They cite one study in which suicide attempters were compared to non attempters on map reading. Attempters were found to be less skilled and may be poorer at problem-solving skills. Another study that they cite indicates that attempters are more likely to procrastinate dealing with problems and that they have difficulties in initiating the process of problem-solving when compared to their non attempter peers (40). Still another study they cite indicates that attempters are more prone to use social isolation as a coping tool.

In their own study done on patients in a psychiatric hospital, divided into three groups and one group of non suicidal patients and still another of attempters at a general hospital, they found a high percentage of girls among the attempters (one group had 69% and

another 78%). Boys were statistically different from the girls in their tendency to blame others for their problems. All those in the psychiatric hospital were found to be significantly higher on social withdrawal. They also conducted a different study based on levels of sadness and found that the more sad group uses the coping strategy of distraction and wishful thinking, while the not so sad group tended to use more cognitive restructuring. Significant differences were seen between genders in studies comparing clinically depressed. The majority of the girls fell into the depressed group and the majority of the boys into the non-depressed group (40). Furthermore, depressed subjects showed significantly more social withdrawal, less cognitive restructuring and more blaming of others. Further analysis showed that social isolation was not particular to suicide attempters, but characteristic of those generally depressed, but it was used more often by suicide attempters.

Suicide and Social Integration

Pete-McGadney (1995) did a study on the self-concept of pregnant teens in different geographic locations and refers to a theory of suicide proposed by Durkheim. This theory postulates that the rate of suicide is affected by two social characteristics. When the rate of social integration is very high it leads to altruistic suicide and when very low it leads to egoistic suicide. Also the rate is influenced by the degree of social regulation. When the rate of social integration is very high it leads to fatalistic suicide and when it is very low to anomic suicide. However, the author states that modern sociologists note that altruistic and fatalist suicides are rare in industrialized societies and translate Durkheim's theory simply into a recognition that "suicide rates are higher when the degree of social integration/regulations is lower" (41). She also reports that the divorce rate in the United States, and Canada are negatively associated with suicide rates. Marriage rates in the States, but not Canada also show a protective affect against suicide when other factors are taken into account. Economic factors where not shown to affect the overall rate, but different societal groupings are effected. She found that social and economic variables are most powerful predictors of the suicide rate for youth. She also reports that these rates are lower in Muslim and Roman Catholic nations. There is a decline in religious practices in Canada which had a rate 50 to 60% higher than the US rate in the eighties (41).

Piacentini *et al*. (1995) link suicide attempts among adolescents to early sexual behavior, substance use, depression, school and legal problems. Data indicates that these problems continue after first attempts and that eventually between 6 and 50% will repeat their attempt with a 5% taking their own lives eventually. Interestingly, these authors report that almost half of these attempters will receive no formal therapeutic services. Secondly, that there is a high attrition rate among those that do, especially among the older youth. Their study indicates that younger males received more treatment than older males or females. Thus age for males is recognized as a significant predictor of the number of treatment sessions kept. They also conclude that age is a predictor among males, that is older youths are at a higher risk (42).

Koopmans (1995) wrote an article on the relation of family dysfunction and teenage suicide attempts. He studied questions of boundary transgression, double bind interactions and the demarcation of kinship roles. Following family systems theory he suggests that suicide is a double bind message in which messages concerning the need for autonomy and the need for parental supervision are simultaneously asserted. Koopmans sees suicide attempts as an intent to make a "first order" change. Furthermore he suggests that many factors previously identified as predictors of suicidal behavior can be interpreted as boundary transgressions such as lack of parental permissiveness with regard to dating. He points out that the recognized predictors such as aggression, depression, ego strength and feelings of helplessness do not contradict family systems perspective that family conflict mediates these factors (43).

Conclusion

Suicide among teens is a growing problem reflecting the complexities and mounting tensions of contemporary society. Much like other psychological phenomena, adolescent suicide is multifactorial requiring a multilevel response from educators, psychologists, social workers, clergy and politicians. Professionals must know and recognize the high risk factors and therapeutic efforts should include coping, problem solving and social skills. Depressive families should be identified and treated appropriately. Young children manifesting depression or the tendency to isolate themselves should be identified and given the necessary training so as to overcome feelings of helplessness and of incompetence.

Prevention programs are needed among adolescents, especially those using controlled substances. The public needs to be educated as to the correlation between alcohol and teen suicide. Laws need to be enforced with regard to the access minors have to alcoholic beverages.

Schools could develop programs helping students to learn social, problem-solving and coping skills. School psychologists and teachers must be trained to recognize victims of child sexual molestation.

Clergy should be educated as to the complexity of sexual identity of young people and the harmful

effects of diatribes and condemnations against homosexuality which often intensify guilt and feelings of worthlessness. Government agencies must become more adept at recording and informing accurately the causes of death so that those responsible for public policies can detect early negative trends and provide the necessary funding for studies and preventive programs.

The media must take responsibility for their programing and be cognizant of the dire consequences of contagion.

More studies are needed. Studies in Puerto Rico on the correlation of suicide rates and natural disasters should be addressed. The military must look into the suicide rates of young Puerto Ricans in the service. Investigations are hampered by government agencies which do not release suicide statistics in a timely way. A study on suicide contagion is needed in Puerto Rico.

Abstracto: *Este artículo revisa la literatura sobre los factores de riesgo que se relacionan al suicidio de adolescentes en los Estados Unidos y Puerto Rico. Los hallazgos incluyen la interacción de multifactores como: la depresión, la homosexualidad —por la hostilidad que enfrentan—, el abuso sexual, la falta de destrezas sociales, entre ellas las de resolver problemas, de estrategias de manejo familiar, sentimientos de aislamiento e incapacidad, contagio, diferencias de género, abuso de alcohol y de sustancias controladas, desórdenes siquiátricos, factores biológicos, al igual que los desastres naturales. En este artículo se presentan estadísticas de prevalencia de suicidio entre los adolescentes y jóvenes militares.*

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Estudios Originales:

Determinación de las Propiedades Psicométricas de la Escala de Depresión Geriátrica (*Yesavage & Brink, 1983*), en una Muestra de Ancianos Puertorriqueños

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Resumen: *La depresión es uno de los desórdenes psiquiátricos más comunes en la población envejecida (2). A pesar de que Puerto Rico es un país con una alta proporción de envejecidos(9.7%), hay muy pocos estudios relacionados a esta población. El propósito de esta investigación es conocer las propiedades psicométricas de la Escala de Depresión Geriátrica(EDG). Así como determinar si la EDG es una medida adecuada para cernir síntomas depresivos en los envejecidos puertorriqueños. En Puerto Rico se ha utilizado indiscriminadamente la Escala de Depresión Geriátrica sin tener estudios sobre las propiedades psicométricas para esta población. A esos efectos se seleccionó una muestra de 146 envejecidos, residentes en égidas del área metropolitana, que tuvieran 65 años o más.*

En los resultados sobre las características psicométricas de la EDG se encontró un coeficiente de consistencia interna Alfa de Cronbach de .83. Con relación a la validez de constructo se encontró una correlación de .72 entre la EDG y el Inventario de Depresión de Beck. Además se realizó un análisis de factores en el que se encontró una estructura factorial de 5 factores que explica un 43.81% de la variación total del instrumento. De acuerdo a estos resultados la EDG parece tener un alto grado de consistencia interna y una buena validez de constructo al compararla con el Inventario de Depresión de Beck.

Introducción

Los ancianos presentan una alta incidencia de problemas emocionales (1). La depresión es uno de los desórdenes psiquiátricos más comunes en la población envejecida (2) y resulta ser una de las mayores causas de hospitalización psiquiátrica en personas sobre 65 años (3). De acuerdo al Instituto Nacional de Salud Mental (INSM), en un estudio epidemiológico realizado en 1984, los síntomas de depresión ocurren en un 27% de los viejos residentes en la comunidad, con un 1% de desórdenes de depresión mayor (4).

Los envejecidos con depresión rara vez buscan ayuda para la misma, por lo que se hace necesario buscar métodos más efectivos para identificar a la población en riesgo. Los instrumentos de evaluación estructurados son útiles en cernir problemas que pueden ser difíciles de reconocer en la población de envejecidos, aun después de ser evaluados clínicamente (5). El manejo de estos instrumentos también ayuda a economizar tiempo, facilitar los procesos de evaluación y mejorar la exactitud y la confiabilidad de la evaluación.

La evaluación clínica de depresión en los envejecidos ha utilizado tradicionalmente una variedad de escalas de auto informe y de observación para conocer la severidad e intensidad de la depresión (6). Los inventarios de auto evaluación, combinados con un historial del paciente y una entrevista, tanto al paciente como a familiares del mismo, ayudan a conocer la severidad, intensidad y duración de los desórdenes depresivos.

Estas escalas para medir la severidad de la depresión son de particular interés para los geropsicólogos por su potencial de costo-efectividad. Su uso es recomendado durante el cernimiento y la entrevista inicial, ya que pueden proveer información sobre las emociones, tan confiable y válida como la obtenida en una entrevista clínica (7). La Escala de Depresión Geriátrica (EDG) fue desarrollada para proveer una medida confiable para cernir sintomatología depresiva en las poblaciones envejecidas, a la vez que fuera de fácil ejecución, se completara en poco tiempo y su administración no necesitase de mucho adiestramiento (8).

En Puerto Rico se han realizado muy pocos estudios relacionados a la depresión en los envejecidos (9,10). Hasta el momento no se tiene una escala de depresión que haya sido construida y validada para los ancianos puertorriqueños. Es importante utilizar escalas

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construidas específicamente para esta población ya que este grupo puede presentar características diferentes a otros. A través de este estudio se desea conocer si la Escala de Depresión Geriátrica, la cual ha sido una de las escalas de auto informe más utilizadas en los envejecidos (11), es una medida efectiva y confiable entre los envejecidos puertorriqueños. La población de envejecidos en Puerto Rico, al ser un sector numeroso y que ha sido identificado como uno de escasos recursos, tanto económicos (12) como de apoyo social (13), de servicios médicos (14) y psicológicos (9,15), se considera un área de importancia.

Método

Participantes

Se seleccionaron 153 participantes, residentes en diferentes égidas en el área metropolitana. Se definió envejecidos como personas de 65 años o más, residentes en alguna égida del área metropolitana.

Para seleccionar las égidas se tomó una muestra de las 34 égidas que componen la región metropolitana y norte I. Estas regiones comprenden los pueblos de San Juan, Guaynabo y Bayamón, según la Oficina de Asuntos de la Vejez. Se seleccionaron estas regiones por las siguientes razones: accesibilidad de las mismas y entre estas dos regiones se concentran más del 52% de los envejecidos residentes en égidas, con 34 de las 84 égidas en Puerto Rico (según la lista preliminar de égidas y estimado de residentes de la Oficina de Asuntos de la Vejez). La muestra se seleccionó por disponibilidad. Luego de obtener la autorización de la administración se procedió a visitar a los participantes orientándolos sobre el estudio. Si accedían a colaborar se completaba la hoja de consentimiento informado.

De los 146 envejecidos en la muestra final, 119 son mujeres (81.5%), mientras 27 son hombres (18.5%). La edad promedio de los participantes fue de 76.5 años. La edad mínima para propósitos del estudio fue de 65 años mientras la máxima fue de 94 años. Con relación al estado civil, el 50.7% de los participantes eran viudos/as, un 29.5% relación consensual, un 27.4% divorciados/as, un 10.3% casados/as y un 9.6% solteros/as. Se encontró que un 61% de los participantes eran católicos y un 30.9% protestantes, mientras un 8.3% profesaban otras religiones.

Instrumentos

Escala de Depresión Geriátrica

La Escala de Depresión Geriátrica (EDG) fue desarrollada por Yesavage, Brink y colaboradores en 1982. La EDG consta de 30 reactivos los cuales exploran tres aspectos relacionados a la depresión: síntomas afectivos, síntomas cognoscitivos y de comportamiento, utilizando un formato de respuesta de Sí o No. La Escala la cual ha sido específicamente diseñada y validada para medir depresión en los envejecidos utiliza un formato de respuesta Sí o No. Se investigó la confiabilidad de la escala, teniendo una consistencia interna (Coeficiente Alfa de Cronbach) de .94 y utilizando el método de división por mitades con .94 (16). Con relación a la consistencia a través del tiempo se obtuvo una correlación de .84 (16). Estos resultados respecto a la confiabilidad de la escala, sugieren un alto grado de consistencia interna.

En el estudio de validación de la escala realizado por Brink, Yesavage y colaboradores(1982), se observó una validez concurrente alta con la Escala de Depresión de Zung con una correlación de .83 y de .84 con la Escala de Depresión de Hamilton (17). Estos resultados van a la par con un estudio piloto realizado en Puerto Rico, en el cual se encontró una correlación de .76 entre la EDG y el Inventario de Depresión de Beck (18). Para esta investigación se utilizó la versión en español, adaptada a la población puertorriqueña (18).

De los 30 reactivos de la EDG, 20 indican la presencia de depresión, si son contestados de manera afirmativa, mientras que los 10 restantes demuestran depresión al ser contestados de manera negativa (16). Para la corrección de la prueba se da un punto por cada respuesta que confirme un síntoma depresivo. La puntuación fluctúa entre: 0-9 no depresión o normal, 10-19 depresión leve y 20-30 depresión severa.

Inventario de Depresión de Beck

Para examinar la validez de constructo de la Escala de Depresión Geriátrica se utilizará el Inventario de Depresión de Beck (BDI). Durante los pasados 25 años el BDI ha sido uno de los instrumentos más frecuentemente utilizados para medir intensidad de depresión en pacientes psiquiátricos (19).

El BDI está compuesto por 21 reactivos, cada uno de los cuales describe una manifestación de depresión y consiste de 4 aseveraciones diseñadas para reflejar el grado de severidad del síntoma. Estos van desde neutral a máxima severidad. La puntuación total del BDI se clasifica entre: 0-9 no depresión, 10-15 depresión leve, 16-19 depresión leve a moderada, 20-29 depresión moderada a severa, 30 ó más depresión severa. Se escogió el BDI como medida de comparación, debido a que esta escala aparenta ser una medida efectiva de depresión para la población envejecida de Puerto Rico. Rosado (1997) realizó un estudio con 80 envejecidos puertorriqueños entre las edades de 65 a 85 años (10). En esta investigación se encontró que el BDI tenía una consistencia interna (alfa de Cronback) de .89. Al estudiar la validez de constructo de este instrumento se encontró una correlación de .90 al comparar los resultados de la prueba con el diagnóstico ofrecido por un psicólogo clínico licenciado con 5 años de experiencia (10).

En el estudio realizado por Bernal, Bonilla y Santiago (1995), utilizando una muestra de 300 participantes del Centro Universitario de Servicios y Estudios Psicológicos (CUSEP) de la Universidad de Puerto Rico, con una edad promedio de 25.25 años, se encontró que los resultados apoyaron la validez del instrumento como medida de sintomatología depresiva (20). Para propósitos de este estudio se incluyó una planilla de datos socio-demográficos, auscultando datos tales como: edad, escolaridad, nivel socioeconómico y estado civil, entre otras.

Procedimiento

Las escalas fueron administradas verbalmente, a pesar que se le ofrecían las opciones de realizarla de manera escrita o verbal. Todos los participantes escogieron la opción de la entrevista verbal indicando que se les dificultaba en la mayoría de los casos por problemas en la visión. El orden de administración de los instrumentos fue variado, a la mitad de los participantes se le entrevistó usando primero la EDG y a la otra mitad usando primero el BDI, esto con el fin de minimizar los efectos del error progresivo. Luego de administrar las pruebas a la muestra, se procedió a realizar los análisis estadísticos, utilizando el programa de computadora SPSS.

Resultados

A continuación se discuten los resultados de los análisis estadísticos para establecer las características psicométricas de confiabilidad y validez para la EDG en una muestra de envejecidos en Puerto Rico. En el análisis de confiabilidad se encontró un coeficiente de consistencia interna alfa de Cronbach de .83. Se realizó otro análisis de consistencia interna utilizando el método de división por mitades, obteniéndose un coeficiente de .82.

Para conocer la validez de constructo se procedió a correlacionar la puntuación en la GDS con la puntuación en el Inventario de Depresión de Beck. En dicho análisis se encontró una correlación de .72 ($p=.000$).

Se realizó un análisis de reactivos para identificar la calidad de los reactivos, utilizando el índice de discriminación (r_{bis}). Los mismos fluctuaron entre .12 y .58, siendo el índice de discriminación promedio .37. En la Tabla 1 se presentan los reactivos con su respectivo índice de discriminación.

Se realizó un análisis de factores con el propósito de abundar sobre la validez de construcción lógica de la escala. De estos análisis se obtuvieron 5 factores con valores Eigen mayores de 1. Estos factores lograron explicar un 43.81% de la variabilidad total del instrumento. En la Tabla 2 se presentan los factores con sus respectivos valores Eigen y la variabilidad explicada por cada uno, mientras en la Tabla 3 se presenta la estructura factorial del instrumento, incluyendo la carga de cada reactivo.

Tabla 1
Índices de discriminación

Reactivos EDG	Indice de discriminación (r_{bis})
1	.43
2	.51
3	.54
4	.19
5	.39
6	.45
7	.28
8	.44
9	.35
10	.33
11	.39
12	.14
13	.32
14	.20
15	.41
16	.58
17	.47
18	.38
19	.12
20	.36
21	.35
22	.49
23	.46
24	.35
25	.42
26	.45
27	.28
28	.36
29	.22
30	.34

Tabla 2
Variación explicada por los factores en la EDG

Factor	Valor Eigen	% variabilidad	% acumulado
1	3.515	11.717	11.717
2	2.677	8.922	20.639
3	2.446	8.154	28.793
4	2.259	7.529	36.322
5	2.247	7.490	43.812

Tabla 3
Estructura factorial de la Escala de Depresión Geriátrica

Factores con sus respectivos reactivos		Carga
Factor 1 Preocupación por el pasado y futuro y ánimo triste		
23	Cree que los demás tienen más suerte.	.578
13	Se preocupa frecuentemente por el futuro.	.575
11	Se siente a menudo intranquilo	.570
8	Tiene miedo de que algo le vaya a pasar.	.548
3	Siente que su vida está vacía.	.536
16	Se siente a menudo triste y desanimado.	.516
2	Ha abandonado muchos intereses y actividades.	.492
10	Se siente incapacitado de realizar actividades.	.468
4	Se siente aburrido frecuentemente.	.467
1	Esta básicamente satisfecho con su vida.	.414
6	Tiene pensamientos que le molestan.	.410
25	Siente frecuentemente deseos de llorar.	.390
18	Se preocupa mucho por el pasado	.333
Factor 2 Falta de energía y aislamiento social		
21	Se siente lleno de energía.	.672
20	Es difícil empezar proyectos nuevos.	.601
12	Prefiere quedarse en casa en vez de salir.	.519
28	Evita relacionarse con otro grupo de personas.	.494
19	Cree usted que la vida es excitante.	.491
Factor 3 Percepción de habilidad cognitiva		
30	Está su mente tan clara como antes.	.680
14	Cree que tiene más problemas con la memoria que las demás personas.	.655
26	Es difícil para usted concentrarse.	.576
27	Disfruta el levantarse por las mañanas.	.371
Factor 4 Visión optimista		
9	Se siente feliz la mayor parte del tiempo.	.730
5	Tiene usted esperanza en el futuro.	.629
29	Le resulta fácil tomar decisiones.	.354
Factor 5 Afecto inestable		
7	La mayoría del tiempo está de buen humor.	.723
17	Se siente inútil, o que no vale nada.	.562
22	Se siente usted sin esperanza.	.489
15	Cree que es maravilloso estar vivo.	.485
24	Se molesta usted por cosas pequeñas.	.380

Se realizó además un análisis descriptivo de las puntuaciones obtenidas por los participantes en las escalas utilizadas. Se encontró que la puntuación mínima de la EDG fue 0 y la máxima fue de 20. La puntuación promedio fue de 5.83 con una desviación estándar de 4.58. Mientras en el Inventario de Depresión de Beck, el valor mínimo fue 0 y el máximo 42, con una puntuación promedio de 12.70 y una desviación estándar de 8.65.

A continuación se discuten las distribuciones porcentuales de los participantes por niveles depresivos, en las dos escalas utilizadas en el estudio. En la EDG se observó que un 84% no presentaba síntomas de depresión (no depresión), mientras un 14% presentaron características de depresión leve y un 1.4% depresión severa. En el BDI se observó que un 37% presentaron puntuaciones que se clasifican como no depresión, un 38% en la categoría de depresión leve, un 8.2% depresión leve a moderada, un 12.3% de moderada a severa y un 4.1% depresión severa.

Discusión

Los resultados relacionados a las características psicométricas de la EDG, adaptada a la población envejecida de Puerto Rico pueden ser considerados como satisfactorios. Al medir la consistencia interna de la prueba utilizando el coeficiente de correlación alfa de Cronbach (.83) y el método de división por mitades (.82) sugieren un alto grado de consistencia interna para la versión en español de la EDG, utilizando los criterios establecidos por Kline(1998) (21). Estos resultados son similares a los encontrados en el estudio piloto realizado en Puerto Rico, con un coeficiente alfa de .86 y un coeficiente de división por mitades de .86 (18). Además comparan de forma satisfactoria con estudios realizados en países como los Estados Unidos y España (11,16,22) .

Con relación a la validez de constructo donde se correlacionó la puntuación en la GDS con la respectiva puntuación en el Inventario de Depresión de Beck, en estas correlaciones se encontró un índice de correlación media alta (.72) utilizando los criterios establecidos por Champion en 1991, el cual considera una correlación moderada alta de .51 a .75. Estos resultados sugieren que la EDG aparenta ser una medida efectiva para cernir síntomas depresivos en la población envejecida de Puerto Rico.

Para evaluar la capacidad discriminatoria de los reactivos se examinaron los índices de discriminación de cada uno de los reactivos, utilizando el criterio para el índice biserial de Ebel (.30 a .75) (1975). Se observó que 23 de los reactivos presentaban índices de discriminación adecuados; mientras que los reactivos 7 y 26 obtuvieron unos índices que se consideran marginales. Los reactivos 4, 12, 14, 19 y 29 tienen unos índices de discriminación considerados bajos, por tanto se considera que dichos reactivos no discriminan adecuadamente.

Finalmente se realizó un análisis de factores para conocer la validez de construcción lógica de la Escala de Depresión Geriátrica con el propósito de identificar el factor o los factores comunes que contribuyen a la varianza total de los resultados. Este análisis de factores se realizó siguiendo las recomendaciones de

Floyd Y Widaman, (1995) (24), los cuales indican que, a pesar de que los métodos de análisis de factores son más claros y fáciles de repetir si la información se comporta con una normalidad multivariada, el supuesto de que los datos deben de distribuirse normalmente puede ser muy estricto y riguroso. A pesar de los problemas estadísticos y conceptuales en el análisis de factores para información dicotómica y siguiendo las recomendaciones de autores como Parmelle, (1989) (25) y Floyd y Widaman (1994) (23), se procedió a realizar el siguiente análisis de factores. Estos resultados deben ser analizados con cautela debido al uso de variables categóricas.

En este análisis se logró explicar un 43.5% de la variación en depresión según medida por la Escala de Depresión Geriátrica. Se identificaron cinco factores. El factor 1 está relacionado con preocupación por el pasado y futuro, y ánimo triste; el factor 2, con falta de energía y aislamiento social. El factor 3 se relaciona con percepción de habilidad cognoscitiva. En el factor 4 se observa visión optimista. Mientras que en el factor 5 se encontró mayor dificultad para establecer una interpretación clínica de los reactivos, relacionándose con afecto inestable.

Tomando en consideración los problemas metodológicos con el uso de análisis de factores para variables dicotómicas y para propósitos de validar la prueba, se le debe dar más peso a los resultados del coeficiente de correlación. Dicho coeficiente indica que las pruebas (EDG y BDI) correlacionan alto al medir el constructo de depresión. De igual forma, los resultados del análisis de reactivos demuestran que, en términos generales, los reactivos de la EDG discriminan adecuadamente. Según lo presentado por Brink, (1992) (26) y Parmelle (1989) (25), donde describen la EDG como una escala unifactorial, se recomienda que se utilice el análisis de factores como una descripción de las posibles manifestaciones clínicas.

En relación a las distribuciones perceptuales de los participantes por niveles depresivos, al observar las puntuaciones en ambas escalas se encontró una puntuación promedio de 5.66, en la EDG, lo cual se clasifica como normal o que no presenta síntomas depresivos. Mientras que en el Inventario de Depresión de Beck se observó una puntuación promedio de 12.47 clasificándose dicho resultado como depresión leve.

Estas diferencias entre los promedios pueden deberse al hecho de que la EDG no incluye reactivos relacionados a medir quejas somáticas. La justificación de los autores para no incluir reactivos dirigidos a problemas físicos en la escala es que no necesariamente estos reactivos proveen un índice real de depresión para esta población. Los envejecidos, por lo general, tienden a informar quejas somáticas las cuales pueden ser producto del proceso de envejecimiento (16). Un ejemplo de quejas somáticas relacionadas con el proceso de envejecimiento son: la fatiga, el insomnio y el estreñimiento. Estas quejas pueden ser encontradas en poblaciones envejecidas no deprimidas (17). Esto se observó en el presente estudio a través de información cualitativa ofrecida por los participantes. Ejemplo de éstas son: "Ya no necesito dormir tanto como antes." "No tengo tanta energía como antes, pero hago lo que puedo."

Entre las limitaciones de este estudio está el que la muestra utilizada para el estudio era una sesgada, ya que sólo participaron en la investigación residentes en égidas del área metropolitana. El hecho de que los participantes fueran residentes en égidas, podría reflejar características exclusivas de esta población. Por tanto, se recomienda que se realicen otras investigaciones a través de toda la isla, con envejecidos en la comunidad en general, en hogares de cuido y en hospitales con el propósito de generalizar los resultados. Otra de las limitaciones del estudio es que los participantes no tenían un diagnóstico de depresión. Se recomienda se realicen estudios utilizando pacientes envejecidos con diagnósticos de depresión, y así determinar la validez discriminante del instrumento y los índices de sensitividad y sensibilidad de la EDG.

En futuras investigaciones sería recomendable realizar entrevistas a personas significativas, las cuales pudieran hacer observaciones sobre la conducta del envejecido y correlacionar esta información con escalas como la EDG.

Se debe continuar estudiando el área de depresión en la población envejecida de Puerto Rico incluyendo estudios comparando poblaciones deprimidas, tanto geriátricas como adultos jóvenes para conocer si presentan un patrón diferente en la expresión de la sintomatología.

Otra de las áreas mencionadas con mayor frecuencia por los envejecidos en la muestra fue la soledad, indicando que esto afecta en gran medida su estado de ánimo. Sería interesante realizar estudios para conocer las necesidades de esta población y cómo pueden atenderse, ya sea ofreciendo información sobre las diferentes facilidades y oportunidades existentes o trabajando con la modificación de actitudes hacia la vejez, tanto de la sociedad en general como en los propios envejecidos.

En Puerto Rico se ha utilizado indiscriminadamente la Escala de Depresión Geriátrica sin tener estudios sobre las propiedades psicométricas para esta población. Con este estudio se aporta conocimiento sobre las propiedades psicométricas de la Escala de Depresión Geriátrica en Puerto Rico. De acuerdo a los resultados encontrados sobre las características psicométricas de la Escala de Depresión Geriátrica,

en la población de envejecidos puertorriqueños la misma parece ser una medida válida y confiable. Esta escala es un cernimiento rápido y clínicamente pertinente, el cual puede ser administrado por personal no especializado en el área de salud mental. El poder identificar envejecidos con alto riesgo de desarrollar síntomas depresivos a través de un instrumento de rápida administración puede resultar muy útil para propósitos de prevención o de referidos a tratamientos de salud mental. Con este estudio se espera ofrecer alternativas para el cernimiento de condiciones de salud mental, a través de un instrumento debidamente validado.

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ASOCIACIÓN MÉDICA DE PUERTO RICO

"Manejo de Problemas Comunes en Pediatría"

Hotel Embassy Suite, Isla Verde
3 de junio de 2000

PROGRAMA

12:00 - 12:55 p.m.	Inscripción y Almuerzo
12:55 - 1:00 p.m.	Bienvenida Dr. Luis A. Parés Martínez *Presidente Asociación Médica de Puerto Rico*
Moderador:	Dr. José Rivera Viera *Presidente Sección de Pediatría AMPR*
1:00 - 1:45 p.m.	"Problemas Respiratorios en Recién Nacidos" Sylvette Soto, MD *Neonátologa*
1:45 - 2:00 p.m.	Preguntas y Respuestas
2:00 - 2:45 p.m.	"Problemas Comunes Gastrointestinales" José Russé, MD *Gastroenterólogo Pediátrico*
2:45 - 3:00 p.m.	Preguntas y Respuestas
3:00 - 3:45 p.m.	"Manejo de un Paciente que Desarrolla Problemas Hemodinámicos In situ" Gilberto Puig Ramos, MD *Intensivista Pediátrico*
3:45 - 4:00 p.m.	Preguntas y Respuestas
4:00 - 4:45 p.m.	"Problemas Comunes de Trauma en Niños" Pablo Marrero, MD *Ortopeda Pediátrico*
4:45 - 5:00 p.m.	Preguntas y Respuestas
5:00 p.m.	Clausura y Coctel

Espacio limitado. Favor confirmar asistencia al 721-6969

Programa organizado por la Sección de Pediatría de la A.M.P.R.

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Estudios Originales:

Desarrollo de la Prueba de Actitudes y Conocimientos sobre la Vejez (PCAV): Estudio piloto sobre su aplicabilidad en Puerto Rico

Jessica Montalvo Toro, PhD
*José Rodríguez, MD, MPH ,PhD **

Resumen: *Esta investigación tuvo el propósito de desarrollar una prueba para medir las actitudes y conocimientos acerca de la vejez con una muestra de 151 estudiantes de bachillerato en enfermería. Se escogieron los estudiantes de primero y cuarto año que estuvieran matriculados en una universidad del área oeste en el programa de Bachillerato de Enfermería. El instrumento utilizado fue la prueba PCAV (Prueba de Actitudes y Conocimientos sobre la Vejez), la cual se compone de dos áreas: Actitudes y Conocimientos. Se realizaron análisis psicométricos en ambas áreas. Además, se realizó un análisis de factores exploratorio con el área de Actitudes. Los resultados demostraron que la prueba PCAV mide cuatro factores en el área de Actitudes: interacción social, preocupación emocional, creencias personales, y discriminación social. Los factores obtuvieron índices de confiabilidad altos (.70 a .73).*

Introduction:

En siglos anteriores existían actitudes negativas hacia la vejez, por ejemplo, en la civilización romana, la vejez era vista como una enfermedad. Muchas de estas actitudes negativas se han mantenido en el siglo XX, y no dudamos que puedan seguir hasta el próximo siglo, a pesar de todos los cambios positivos que han traído para la sociedad la modernización e industrialización. Usualmente, a quienes han favorecido estos cambios ha sido a los adultos jóvenes y, por consiguiente, los envejecidos han sido considerados como un grupo no privilegiado en nuestras últimas décadas. A pesar de todos los problemas que ha afrontado la población de envejecidos, es el grupo que más ha crecido en los Estados Unidos. En Puerto Rico la situación es similar, como se observará más adelante. Además, los envejecidos son el grupo de edad (65 años en adelante) que más acude a agencias públicas y privadas para recibir algún tipo de servicio (1, 2). Uno de los servicios que nuestros ancianos más utilizan son los servicios médicos (3, 4, 5).

En este trabajo se realizó una revisión de investigaciones recientes que demuestran un déficit de conocimiento por parte de los profesionales de la salud, especialmente las enfermeras, hacia la etapa de la vejez, que en este trabajo será definida como aquella etapa de edad de los 65 años en adelante. Es de suma importancia realizar investigaciones sobre la población de envejecidos porque se está observando un cambio demográfico severo tanto en los Estados Unidos como en Puerto Rico (6, 1, 7, 8, 9, 10, 11, 12, 13). La población de envejecidos se considera como el grupo de edad que más rápidamente ha crecido en los Estados Unidos. Se proyecta que para el año 2000 el número de ancianos va a aumentar a 35 millones y a casi 70 millones para el año 2030 (6). En 1990 de los 31.2 millones de personas de 65 años de edad o más en los Estados Unidos, el 32 por ciento estaba compuesto de personas entre las edades de 75 a 84 años; y otro 10 por ciento de 85 años en adelante (1).

En Puerto Rico, al igual que en los Estados Unidos, se observa un aumento en la población de ancianos. De una población censal de aproximadamente 3.5 millones, el 10 por ciento lo compone el grupo de 65 años en adelante. Se estima que para el año 2020 aumente a 20.8 el porcentaje de la población de 65 años en adelante. Las razones de este aumento en la población anciana son varias. Por ejemplo, avances en conocimiento médicos que mejoran la supervivencia, mejoramiento práctico de saneamiento, eliminación de serias enfermedades infecciosas, reducción en la mortalidad infantil, reducción en las tasas de nacimientos, menos mujeres muriendo durante el parto y aumento en la importancia que se da a los ejercicios y la nutrición. En Puerto Rico, además de los factores mencionados anteriormente, también el factor de migración contribuye en algún grado al aumento de la población anciana (11). La emigración ha venido a ser un factor que ha acelerado la concentración de la población envejecida al haber una concentración relativamente alta de emigrantes que optan por

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finalizar sus días en nuestro país. De igual forma, los hijos de estos migrantes tendrán un efecto demográfico, ya que éstos, aun cuando inicialmente aumentarán la base de la pirámide poblacional, de quedarse en el país envejecerán, aumentando la población de ancianos (14,15). Sin lugar a dudas, debemos comenzar a estudiar nuestra población de ancianos y nuestro conocimiento y actitudes hacia ellos.

Existen diferentes medidas para evaluar las actitudes y los conocimientos sobre los ancianos (6, 15, 16, 17, 18). Los instrumentos más utilizados en las investigaciones gerontológicas son el FAQ ("Facts on Aging Quiz"), OPS ("The Old People Scale") y "Oberleder Attitude Toward Aging Scale". Aunque existen diferentes pruebas y escalas que miden actitudes y conocimientos hacia la vejez, en Puerto Rico se carece de un instrumento válido y confiable para este fin. Por tal razón, uno de los propósitos primordiales de este trabajo fue desarrollar una prueba que mida las actitudes hacia nuestros ancianos y los conocimientos básicos que se tienen sobre esta subpoblación puertorriqueña. Además, en este estudio se investigó si existe una falta de conocimiento añadida a actitudes negativas y conceptos erróneos acerca de la vejez por parte de un grupo de estudiantes de enfermería en el área oeste de Puerto Rico.

Método

Participantes

Los participantes en este estudio fueron 151 estudiantes de enfermería del área oeste. El 60% de la muestra estuvo compuesta por los estudiantes de primer año (91 estudiantes) y el 40% (60 estudiantes) por el grupo de cuarto año. De la muestra total hubo 84% mujeres y 13% hombres. En términos más específicos, el grupo de primer año estuvo compuesto por 87% mujeres y 13% hombres; el grupo de cuarto año, a su vez, estuvo compuesto por 80% mujeres y 20% hombres. El promedio de edad de la muestra fue de 22 años, fluctuando ésta desde 17 años hasta 46 años. El promedio de créditos aprobados por los estudiantes de primer año fue de 37 créditos. Los estudiantes de cuarto año tenían un promedio de 124 créditos aprobados. Se decidió utilizar el campo de la enfermería porque el estudio de Miranda (5) demostró que, en relación con el uso de servicios médicos, el 95% de los envejecidos puertorriqueños indicó ser atendidos por un enfermera/o.

Materiales

El instrumento de investigación fue la Prueba de Conocimiento y Actitudes sobre la Vejez (PCAV), que fue desarrollada por la autora de este trabajo.

Propósito de la prueba

La prueba PCAV fue desarrollada para medir primeramente el conocimiento que tienen los estudiantes de enfermería sobre la etapa de la vejez. Segundo, mide el gradiente de "ageism" (estereotipos negativos hacia la vejez) a través de respuestas incorrectas que son dadas por el que contesta la prueba y, por lo tanto, ofrece en esta línea información sobre las actitudes que posee la persona sobre la vejez.

Descripción de la prueba

La prueba PCAV consta de un total de 70 reactivos. La prueba fue dividida en dos categorías: 40 reactivos en Conocimiento y 30 reactivos en Actitudes. La categoría de "conocimiento" tuvo un formato tricótomo, ya que además de cierto o falso se presentó la opción de "no sé" con el propósito de evitar que el participante trate de adivinar la respuesta correcta. Estos reactivos evalúan conocimiento gerontológico en las siguientes áreas: salud, aspectos sociales, económicos y psicológicos. En la categoría de "actitudes" el formato fue tipo Likert del 1 a 5 para los 30 reactivos, los cuales miden aspectos psicológicos y sociales.

Procedimiento

Procedimiento para desarrollar la prueba

Se desarrolló un total de 212 reactivos, lo cual se sometió a un panel de jueces, utilizando el método cuantitativo de Lawshe (1978). El criterio de selección de los reactivos fue de un 75% o más de acuerdo entre los jueces; esto es conocido como el CVR ("content validity response"). También se computó el CVI ("content validity index"), lo cual se refiere al promedio de los valores CVR de los reactivos seleccionados. El propósito de este procedimiento fue poder escoger, entre los 212 reactivos, los 40 reactivos en la parte de Conocimiento y 30 reactivos en la parte de Actitudes más adecuados.

Diseño de Investigación

El diseño de este estudio fue uno cuasi-experimental por las razones que se expondrán a continuación. Primero, la muestra no fue seleccionada aleatoriamente, sino por disponibilidad. Segundo, no se pudo controlar todas las variables que se presentaron en el momento de administrar el instrumento. Tercero, se administró el instrumento en un escenario natural, en este caso el salón de clases de los estudiantes de enfermería.

Análisis estadísticos

Se utilizó el Análisis de Factores exploratorio para la prueba en el área de Actitudes. El propósito fue evaluar la validez de constructo de la misma o cuán adecuado es el reactivo para medir lo que se pretende. Como parte de este procedimiento, se llevó a cabo un análisis de componentes principales con rotación "varimax". Este método de rotación se utiliza cuando los factores no correlacionan entre sí. Se calculó el análisis de coeficiente alfa para obtener la confia-

bilidad de consistencia interna entre los reactivos, tanto del área de Conocimiento como del área de Actitudes. Además, se hizo un análisis de discriminación para obtener las características de los reactivos que componen el área de Conocimiento.

Resultados

En el área de Conocimiento la validez de contenido mediante el método de Lawshe fue de .93. El método de coeficiente alfa, el cual determina la consistencia interna de una prueba a través de los reactivos de la misma reflejó una confiabilidad de .81. Esto indica que los reactivos pertenecientes a la categoría de Conocimientos se relacionan entre sí y, por ende, se relacionan con el concepto general de conocimiento sobre los procesos de envejecimiento.

En la categoría de Actitudes se obtuvo una validez de contenido de .88. Los resultados del análisis de factores reflejaron la existencia de cuatro factores principales. El primer factor —denominado Interacción Social— obtuvo un valor eigen de 4.6, explicando un 15.3% de variabilidad. El segundo factor —Preocupación Emocional— obtuvo un valor eigen de 2.5, explicando el 8.5% de variabilidad. El tercer factor —Creencias Personales— obtuvo un valor eigen de 2.0, explicando un 6.7% de variación. Por último, el cuarto factor —Discriminación Social— obtuvo un valor eigen de 1.8, explicando un 6.1% de la variación. Un 36.7% de la variación total se atribuye a los cuatro factores.

Un total de ocho (8) reactivos obtuvieron una carga inicial igual o mayor a .30 en el factor 1; cinco (5) reactivos obtuvieron una carga inicial igual o mayor a .30 en el factor 2. En el factor 3 ocho (8) reactivos obtuvieron una carga inicial igual o mayor de .30; y tres (3) reactivos obtuvieron un factor de carga inicial igual o mayor a .30 en el factor 4.

Los 24 reactivos seleccionados a través del análisis de factores fueron analizados para establecer los niveles de confiabilidad (ver Tabla 1). De los cuatro factores que componen la categoría de Actitudes de la prueba PCAV, la Discriminación Social reflejó la mayor consistencia interna (.73); mientras que la subescala de Creencias Personales reflejó la menor consistencia interna (.56). El alfa total de la prueba PCAV en el área de Actitudes fue de .57.

Tabla 1
Coeficientes de consistencia interna de cada factor en la categoría de Actitudes de la prueba PCAV

Factor	*Coeficiente alfa de Cronbach*
Interacción Social	0.70
Preocupación Emocional	0.70
Creencias Personales	0.56
Discriminación Social	0.73
Total PCAV Actitudes	0.57

Discusión

Los resultados encontrados en la categoría de conocimientos reflejaron, en los análisis de confiabilidad, índices altos y positivos (alfa de .81). Este resultado sobrepasó, por ejemplo, la prueba FAQ (.28) desarrollada por Palmore (15) y el FAQ-selección múltiple (.36) modificado por Harris y Changas (16). Es importante mencionar que los anteriores instrumentos, a pesar de tener coeficientes alfa bajos, son de las pruebas más utilizadas para evaluar niveles de conocimiento sobre la vejez. Por lo tanto, el PCAV, en el área de conocimiento, refleja ser más confiable al compararlo con otras pruebas existentes que miden conocimiento general sobre la vejez. Los resultados sugieren que el PCAV, área de conocimientos, es un instrumento que consta de un conjunto de reactivos homogéneos y de buena calidad. Esto demuestra que la medición en el área de conocimientos es confiable, por tener una excelente consistencia interna.

En la categoría de Actitudes la validez de constructo fue examinada mediante un Análisis de Factores. El propósito del análisis de factores es reducir y organizar un grupo de reactivos en factores. Un factor es un grupo de reactivos que tienden a relacionarse entre sí. Los resultados, en la categoría de actitudes, arrojaron cuatro factores: Interacción Social (8 ítemes), Preocupación Emocional (5 ítemes), Creencias Personales (8 ítemes) y Discriminación Social (3 ítemes). El Factor 1 fue denominado Interacción Social porque aparentemente mide los contactos que la muestra tiene con la población envejecida, y también su percepción hacia su propia vejez. Las personas que obtienen puntuaciones altas en esta área demuestran una interacción positiva con viejos/as, tanto con familiares como los de la comunidad. También perciben la vejez como una etapa de cambios positivos en el área social y psicológica.

El Factor 2 fue denominado Preocupación Emocional porque los reactivos evalúan asuntos más internos y personales en términos de la vejez. Todos los reactivos arrojaron aspectos psicológicos que los individuos pueden confrontar durante la etapa de la vejez. Una puntuación alta en esta área puede reflejar una actitud negativa hacia su propia vejez y un nivel de preocupación y ansiedad elevada hacia dicha etapa.

El Factor 3 fue denominado Creencias Personales porque la mayoría de los reactivos reflejan mitos que existen en la sociedad sobre los envejecidos. Por

ejemplo, "los ancianos se involucran más en la religión"; "el empleado de edad avanzada se ausenta más en el trabajo, al compararlo con el trabajador más joven". Puntuaciones altas en esta área pueden reflejar la existencia de creencias falsas sobre la edad avanzada.

El Factor 4 fue denominado Discriminación Social. Los reactivos que se agrupan en este área demuestran las actitudes, mayormente negativas, que prevalecen en la sociedad respecto a la vejez. Esta área toma en consideración la percepción que puede tener la persona acerca de cómo se trata socialmente al viejo/a, tanto en el ámbito laboral como en la comunidad. Una puntuación alta refleja que la persona es consciente de la discriminación que existe hacia los viejos/as.

La categoría de actitudes también demostró ser confiable por tener una buena consistencia interna, fluctuando entre .70 a .73; con la excepción del factor 3 (.56), lo cual sugiere menos homogeneidad entre esos reactivos. El alfa total de la prueba PCAV en el área de Actitudes, fue de .57; este resultado no es un índice alto según los estándares establecidos. Sin embargo, Kazdin (19), menciona que el propósito de las medidas de consistencia interna es evaluar el grado en que los reactivos de una prueba miden el mismo dominio de una escala en específico. Por consiguiente, una prueba que es diseñada para medir diferente escalas puede obtener estimados bajos de confiabilidad y, por lo tanto, la prueba no tendrá consistencia interna alta. La prueba PCAV, área de Actitudes, consta de cuatro factores independientes el uno del otro y por tal razón reflejó un coeficiente alfa total moderado. En general, el PCAV se puede considerar una prueba útil para examinar los conocimientos y actitudes prevalecientes hacia la población envejecida puertorriqueña en los estudiantes de primero y cuarto año de enfermería.

Limitaciones

Las investigaciones relacionadas con la conducta humana intentan controlar todas las situaciones o circunstancias que pueden tener algún efecto en los hallazgos. La realidad es que lo anterior es de carácter utópico, pues existen múltiples limitaciones durante el transcurso de una investigación que pueden influir en la obtención de resultados fidedignos. El estudio presente no es una excepción, aunque se debe visualizar las limitaciones como un intento de llevar a cabo futuras investigaciones con el fin de mejorar la presente.

Una limitación en esta investigación fue el hecho de que sólo se pudo obtener la muestra por disponibilidad. Por consiguiente, los resultados con respecto a la validez y confiabilidad de la prueba PCAV y las actitudes y conocimientos sobre la vejez están limitadas a la muestra de estudio. Sugerimos, pues, que se administre la PCAV a otras muestras para continuar explorando su validez y confiabilidad.

Una segunda limitación fue que no se pudo llevar a cabo un estudio de confiabilidad en términos longitudinales, mediante una segunda administración. Sólo se obtuvo la confiabilidad del instrumento mediante la utilización del Coeficiente Alfa de Cronbach, el cual estima la confiabilidad a través de sus elementos constituyentes.

Conclusiones

Una de las aportaciones que se espera hacer con el presente estudio es la utilización de la prueba PCAV para evaluar los conocimientos y actitudes hacia la vejez. El proceso de confiabilidad y validación del PCAV sugiere que la misma aparenta ser válida y confiable para medir los conocimientos y las actitudes hacia la vejez. Se observó a través de los resultados que los estudiantes que formaron parte de la muestra no están fuera de la realidad cuando señalaron que la actitud que tiene la sociedad hacia la vejez es negativa. Además, que la sociedad puede influir en la actitud que puede tener un anciano hacia su propia vejez. Esta aseveración concuerda con Festinger (20) al sugerir que las actitudes se forman de acuerdo con un principio de armonía. Por lo tanto, un cambio en actitud no puede realizarse a menos que el ambiente o sociedad apoye el cambio conductual que acompaña el cambio en actitud.

La literatura ha señalado a la población envejecida puertorriqueña como la más creciente y, a la misma vez, el grupo que más se mal-interpreta (18,6,5,10,11). Por tal razón, se necesita realizar investigaciones sobre esta población e implantar programas educativos en los diferentes currículos universitarios para educar a los futuros profesionales de la salud acerca de la vejez. De esta forma se podrá ofrecer un servicio adecuado que tanto nuestros viejos/as necesitan y merecen.

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– One 10 mg tablet daily for effective symptom relief

Also Proven in Chronic Idiopathic Urticaria

– 24-hour efficacy in treating troublesome CIU symptoms

In controlled clinical trials in seasonal allergic rhinitis patients using the recommended dose, the incidence of headache (12%), somnolence (8%), fatigue (4%), and dry mouth (3%) with CLARITIN® was similar to that of placebo (11%, 6%, 3%, and 2%, respectively).

Once-a-day



Please see next page for brief summary of Prescribing Information.

CLARITIN®
brand of loratadine
TABLETS, SYRUP, and RAPIDLY-DISINTEGRATING TABLETS

Brief Summary (For Full Prescribing Information, see package insert).

INDICATIONS AND USAGE: CLARITIN is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 6 years of age or older.

CONTRAINDICATIONS: CLARITIN is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

PRECAUTIONS: General: Patients with liver impairment or renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (10 mg every other day). (See **CLINICAL PHARMACOLOGY: Special Populations.**)

Drug Interactions: Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n = 24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT_c intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table:

Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg Q8h)	+ 40%	+46%
Cimetidine (300 mg QID)	+103%	+ 6%
Ketoconazole (200 mg Q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of CLARITIN is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m^2 basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m^2 basis).

Pregnancy Category B: There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m^2 basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN should be used during pregnancy only if clearly needed.

Nursing Mothers: Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN is administered to a nursing woman.

Pediatric Use: The safety of CLARITIN Syrup at a daily dose of 10 mg has been demonstrated in 188 pediatric patients 6-12 years of age in placebo-controlled 2-week trials. The effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in this pediatric age group is based on an extrapolation of the demonstrated efficacy of CLARITIN in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparison of the pharmacokinetics of CLARITIN in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of CLARITIN in pediatric patients under 6 years of age have not been established.

ADVERSE REACTIONS: CLARITIN Tablets: Approximately 90,000 patients, aged 12 and older, received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day varied from 2 weeks' to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2% in both the treated and placebo groups.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF MORE THAN 2% IN PLACEBO-CONTROLLED ALLERGIC RHINITIS CLINICAL TRIALS IN PATIENTS 12 YEARS OF AGE AND OLDER

PERCENT OF PATIENTS REPORTING

	LORATADINE 10 mg QD n = 1926	**PLACEBO** n = 2545	**CLEMASTINE** 1 mg BID n = 536	**TERFENADINE** 60 mg BID n = 684
Headache	12	11	8	8
Somnolence	8	6	22	9
Fatigue	4	3	10	2
Dry Mouth	3	2	4	3

Adverse events reported in placebo-controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of nonwhite subjects was relatively small.

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets): Approximately 500 patients received CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with CLARITIN Tablets and placebo.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) did not result in an increased reporting frequency of mouth or tongue irritation.

CLARITIN Syrup: Approximately 300 pediatric patients 6 to 12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 8-15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg daily was less than 1%.

ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF ≥ 2% IN LORATADINE SYRUP-TREATED PATIENTS (6-12 YEARS OLD) IN PLACEBO-CONTROLLED TRIALS, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP

PERCENT OF PATIENTS REPORTING

	LORATADINE 10 mg QD n = 188	**PLACEBO** n = 262	**CHLORPHENIRAMINE** 2-4 mg BID/TID n = 170
Nervousness	4	2	2
Wheezing	4	2	5
Fatigue	3	2	5
Hyperkinesia	3	1	1
Abdominal Pain	2	0	0
Conjunctivitis	2	<1	1
Dysphonia	2	<1	0
Malaise	2	0	1
Upper Respiratory Tract Infection	2	<1	0

In addition to those adverse events reported above (≥ 2%), the following adverse events have been reported in at least one patient in CLARITIN clinical trials in adult and pediatric patients:

Autonomic Nervous System: Altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

Body As A Whole: Angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, viral infection, weight gain.

Cardiovascular System: Hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

Central and Peripheral Nervous System: Blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

Gastrointestinal System: Altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, nausea, stomatitis, toothache, vomiting.

Musculoskeletal System: Arthralgia, myalgia.

Psychiatric: Agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria.

Reproductive System: Breast pain, dysmenorrhea, menorrhagia, vaginitis.

Respiratory System: Bronchitis, bronchospasm, coughing, dyspnea, epistaxis, hemoptysis, laryngitis, nasal dryness, pharyngitis, sinusitis, sneezing.

Skin and Appendages: Dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, rash, urticaria.

Urinary System: Altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; and seizures.

OVERDOSAGE: In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the Tablet formulation (40 to 180 mg). Extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10 mg of CLARITIN Syrup. In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

No deaths occurred at oral doses up to 5000 mg/kg in rats and mice (greater than 2400 and 1200 times, respectively, the maximum recommended human daily oral dose on a mg/m^2 basis). Single oral doses of loratadine showed no effects in rats, mice, and monkeys at doses as high as 10 times the maximum recommended human daily oral dose on a mg/m^2 basis.



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Rev. 1/99 19628434T-JBS

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) are manufactured for Schering Corporation by Scherer DDS, England.

U.S. Patent Nos. 4,282,233 and 4,371,516.

Artículos de Revisión:

El Consentimiento Informado

Juan Rafael Iturregui-Pagán, MD, JD[1]

Según Prosser,[2] consentir se puede definir como simplemente el deseo de que algo ocurra.

La obligación de obtener un consentimiento para cualquier procedimiento o tratamiento médico se basa en la premisa de que la integridad del ser humano es sagrada y en la sociedad contemporánea no se le reconoce la facultad a nadie para interferir con esa integridad personal si el individuo no ha prestado su consentimiento para ello, sea éste uno expreso o tácito. El Tribunal Supremo de los Estados Unidos[3] estableció que:

> *No right is held more sacred, or is more carefully guarded, by the common law, than the right of every individual to the possession and control of his own person, free from all restraints or interferences of others, unless by clear and unquestionable authority of law.*

Son estos principios fundamentales los que permiten establecer que una persona tiene que consentir para que un médico pueda darle un tratamiento; pero, para que ese consentimiento sea válido, el paciente tiene que adquirir un grado de conocimiento razonable de las circunstancias que rodean y median en ese tratamiento. Esto es lo que conocemos como el *CONSENTIMIENTO INFORMADO.*

Pero, ¿qué grado de información es la que tiene que proveer el facultativo para que el consentimiento sea uno informado? ¿Qué criterios deberá tomar el juzgador de los hechos en un tribunal antes de determinar si el consentimiento fue uno informado o no?

Es nuestro propósito presentar los requisitos que rigen en Puerto Rico para determinar qué, ante el juzgador de los hechos, debe considerarse un consentimiento informado.

Antecedentes

En la medicina antigua no sólo no se le ordenaba a los médicos a informarle a sus pacientes sobre los tratamientos que iba a emplear, sino que de hecho se le prohibía. Hipócrates, el Padre de la Medicina, le aconsejaba a los facultativos a esconderle la mayoría de las cosas a los pacientes y a no revelarles nada de su condición presente o futura. Esta actitud influenció en gran manera la medicina occidental y arábiga.[4]

Durante el siglo xviii, aunque se entendía que los pacientes deberían conocer de su tratamiento médico, prevalecía la teoría de que éstos no deberían tomar parte en el proceso decisional sobre su condición, filosofía que influyó en la adopción del Código de Ética Profesional de la Asociación Médica Americana de 1847. Según ésta, se advertía a los médicos a no comunicar pronósticos pobres a menos que fuera estrictamente necesario.[5]

No fue sino hasta principios del presente siglo que fue desarrollándose la teoría de la necesidad de obtener autorización del paciente antes de administrar cualquier tratamiento médico.

Aquellos que se oponían a la doctrina del consentimiento informado insistían que al promover estos valores individualistas se socavan otros valores: se perdía tiempo valioso que era necesario para administrar cuidados a pacientes enfermos, en parte debido al hecho de que el paciente promedio no entiende la información que se le provee o porque el paciente promedio no quiere ser informado; además de que socava la confianza que el paciente debe tener en su médico y, por último, que requerir darle información al paciente de riesgos o fallas en el tratamiento podría tener como resultado que dichas complicaciones ocurran inducidas psicológicamente: la llamada *"psychologically induced self-fulfilling prophesy"*.[6]

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[1] El autor, quien es urólogo con práctica en Mayagüez y Ponce, agradece al Lcdo. Miguel A. Arzola-Barris la revisión del manuscrito.
[2] W. Prosser, *Handbook of the Law of Torts*, §18 (1971).
[3] *Union Pacific Ry. v. Sanford*, 141 US 250, 251 (1973)
[4] 2 Hippocrates, Decorum 297, 299 (W.H.S. Jones, trans., 1959) según citado por Halle Fine Terrion, *Informed Choice: Physicians' Duty to Disclose Nonreadily Available Alternatives*, 43 W. Res. L. Rev. 491, 496 (1993) y por Rich, B., *Advance Directives*, The Journal of Legal Medicine, 19:1, 1998, p. 65.
[5] El Código advertía a los médicos a no hacer pronósticos tristes (*gloomy*) a menos que fuera absolutamente necesario; y cuando fuera necesario, delegar la responsabilidad en una persona de suficiente juicio y delicadeza.
[6] Alan Meisel, *The "Exceptions" to the Informed Consent Doctrine: Striking a Balance Between Competing Values in Medical Decisionmaking*, 179 Wil. L. Rev. 413, 414-416 (1979).

Por otro lado, aquellos que proponían la necesidad de un consentimiento entendían que esa doctrina es el guardián del individualismo en el contexto médico y protegería el derecho del paciente a determinar su propio destino en asuntos médicos. Además, promueve su *status* como ser humano autónomo, protegiéndolo contra abusos por parte de los médicos; protege su integridad física y psíquica y por tanto su privacidad, y le da derecho a obtener compensación por consecuencias dañinas acaecidas por razón del tratamiento médico.

Esta última tendencia fue ganando adeptos, situación que fue reflejándose a través de las normas que fueron adoptando los tribunales (*Mohr v. Williams*, 104 N.W. 12 (Minn. 1905), *Pratt v. Davis*, 118 Ill App 161,166, 79 N.E. 562,564 (1906), entre otros).

El Juez Cardozo[7] en *Schloendorff v. Society of New York Hospital*, 211 NY 125, 105 N.E. 92,93 (1914), jurisprudencia ésta que se considera piedra angular en la adopción de la doctrina del consentimiento informado, reconoció el derecho de un demandante a recobrar daños por un procedimiento no autorizado. Dijo el Juez Cardozo:

> *Every human being of adult years and sound mind has the right to determine what shall be done with his own body; and a surgeon who performs an operation without his patients's consent commits an assault, for which he is liable in damages.*

De ahí en adelante los tribunales fueron adoptando la doctrina de la necesidad de obtener consentimiento antes de poder llevar a cabo cualquier procedimiento invasivo (*Salgo v. Leland Stanford*, 317 P 2nd 170,181 (Cal. 1957), *Natatson v. Kline*, 350 P 2nd 1093, 1104 (Kan. 1959).

Aunque al principio la doctrina del consentimiento informado se fue desarrollando a partir de los casos en que se imponía responsabilidad civil por tratamientos no autorizados catalogándolos como agresión civil (*battery*) (*Montes v. FSE*, 87 D.P.R. 199, 202 (1963)), se fue modificando al entenderse que la causa de acción en aquellos casos en los cuales no ha mediado el consentimiento tiene los mismos requisitos que los necesarios para determinar negligencia profesional (*Ríos Ruiz v. Mark*, 119 D.P.R. 816, (1987)), por lo que el demandante tendrá que demostrar que:

(1) el facultativo tenía una obligación de dar cierta información;
(2) no dio esa información;
(3) el demandante sufrió daños compensables;
(4) si se le hubiera provisto de esa información, una persona razonablemente prudente no hubiera autorizado el tratamiento;
(5) la falta de información fue la causa próxima del daño.

En los Estados Unidos se han desarrollado dos criterios que puede usar el juzgador de los hechos para determinar si hubo o no un consentimiento informado. Veamos.

El criterio del estándar profesional, admitido en la mayoría de las jurisdicciones, establece que la extensión y tipo de información que el médico tiene que poner a la disposición del paciente para que pueda haber un consentimiento informado depende de lo que un médico razonable de la comunidad hubiera informado a su paciente. Esto quiere decir que el proveedor del servicio de salud no está obligado a dar aquella información que un proveedor razonable no daría bajo circunstancias similares. La obligación del médico es un asunto de juicio y discreción profesional.

Los proponentes de este criterio sostienen que solamente el profesional de la salud puede estimar los efectos psicológicos que la información sobre la condición médica o el tratamiento tendrían sobre un paciente en particular. Es más, afirman que amarrar al profesional a un estándar lego en cuanto a la información que tiene que poner a disposición de su paciente interferiría con su discreción médica y a la misma vez "requiere que el tribunal se adentre en las impredecibles complejidades del proceso decisional humano" (*Sepúlveda de Arrieta v. Barreto Domínguez*, 94 CA 139, Opinión del 23 de diciembre de 1994, p. 830).

Por otro lado, encontramos el estándar del paciente razonable, también llamado por algunos tratadistas, como por ejemplo Lane,[8] el Estándar del Riesgo Material (*Material Risk Standard*). Éste estándar requiere que el profesional le dé al paciente aquella información que una persona estimaría pertinente y necesaria para tomar una decisión sobre si someterse o no al tratamiento propuesto. Los tribunales que han adoptado este estándar reconocen que la protección del derecho del paciente a la libre determinación, piedra angular de la doctrina del consentimiento informado, obliga a que el médico le dé a su paciente toda la información que necesite sobre los riesgos del tratamiento propuesto y las alternativas terapéuticas disponibles a la ciencia médica.

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[7] .
[8] M. Lane, Largey v. Rothman, 41 Rutger L. Rev. 705, 1988- 1989, p. 710.

El enfoque no es lo que el médico estima que es beneficioso para su paciente en términos de la información que necesita para hacer una decisión informada, sino qué información debe tener el paciente antes de decidir inteligentemente el someterse a un tratamiento dado.

Bajo este criterio, tanto la materialidad de los riegos como las alternativas disponibles son esenciales al determinar cuánta información está obligado a proporcionar el profesional. Un riesgo material (*material risk*) es aquel que el médico sabe o debería saber es pertinente para que una persona razonable[9] o el paciente en particular, según haya sido adoptado el criterio objetivo o el criterio subjetivo, pueda hacer una decisión inteligente.

En Puerto Rico, la fuente estatutaria que rige este tipo de análisis es la ley que reglamenta el funcionamiento de facilidades de salud, Ley 101 del 26 de junio de 1965, según enmendada por la Ley 150 del 20 de julio de 1979. Esta ley ordena que el Departamento de Salud adopte un reglamento para implementar sus disposiciones. A estos fines, el 30 de mayo de 1985 el Secretario de Salud aprobó el Reglamento 52, mejor conocido como el Reglamento para el Funcionamiento y Mantenimiento de Facilidades de Salud en Puerto Rico. Este Reglamento fue enmendado tanto en 1988 como en 1989 por los Reglamentos 69 y 62 respectivamente.

En el asunto que nos ocupa, el Capítulo 22, Artículo 5, Sección 1 del Reglamento 52, establece que:

> El expediente clínico deberá contener evidencia escrita de un consentimiento *bien* informado para tratamiento y para los procedimientos que se ofrezcan al paciente, en cualquier unidad de servicio de la facilidad. ...
>
> El consentimiento deberá contener, por lo menos: nombre completo del paciente, fecha y hora en que se toma, nombre de la persona que consiente el tratamiento, bien sea el paciente o representante legal, nombre del profesional que examinará, evaluará, diagnosticará y ofrecerá el tratamiento. *Evidencia que demuestre que al paciente se le ha explicado y que éste entiende el contenido del consentimiento; ...*
>
> El consentimiento para procedimientos médicos debe contener además, procedimientos o tratamientos a ofrecerse; autorización para anestesia... posibles riesgos y otras alternativas de tratamiento, y la firma del médico que explica y toma el mismo. (Énfasis nuestro)

En *Ríos v. Mark, supra,* la Juez Asociada Naveira de Rodón, en su voto particular, proponiendo el criterio profesional, expresó:

> Bajo las circunstancias de este caso, antes de imponer responsabilidad al Dr. Mark por haber faltado a su deber de información, era necesario probar que existía ese deber de información como práctica prevaleciente en la comunidad médica.[10]

Un año más tarde, en *Rodríguez Crespo v. Hernández,* 121 D.P.R. 639 (1988), un caso en el que se demanda a un médico por haber ligado un uréter y la subsiguiente pérdida del riñón, luego de una cirugía ginecológica, el Tribunal Supremo adoptó el criterio de materialidad estableciendo que:[11]

> La doctrina del consentimiento informado impone al médico el deber de informar a su paciente acerca de la naturaleza y riesgos de un tratamiento médico propuesto, de manera que el paciente se encuentre en la posición de hacer una decisión inteligente e informada.

De igual forma, citando a *Canterbury v. Spence,* 464 F.2d 772 (D.C. Cir. 1972) añadió:[12]

> La doctrina moderna establece que el médico le debe revelar a su paciente toda aquella información que, de acuerdo con su conocimiento y experiencia, necesitaría conocer el paciente por ser pertinente a la decisión que debe tomar en cuanto a consentir o no a someterse al procedimiento médico propuesto.

Continúa el Tribunal:

> El médico tiene la obligación de divulgarle al paciente los riesgos razonables previsibles, así como los beneficios de tratamientos y procedimientos invasivos del cuerpo humano y de las alternativas disponibles. También debe informar al paciente sobre los riesgos razonables relacionados a no tratarse la condición.
>
> Sin embargo, el médico no es responsable por no divulgar riesgos que razonablemente no pueda prever o por no informar de alguna secuela inesperada que surja durante la cirugía.[13]

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[9] Canterbury, *infra,* p. 783-784.
[10] Ibíd. p. 848.
[11] Ibíd. p. 663.
[12] Ibíd. p. 664.
[13] Ibíd. p. 664.

Continúa el Tribunal:

> En general, el médico debe divulgar aquella información que él razonablemente crea o deba saber que genere un riesgo. Ello no significa que deba comunicar aquellos riesgos de los cuales un paciente promedio estaría advertido o sobre aquellos que el paciente particular haya descubierto por haber sido sometido a un tratamiento similar en el pasado.[14]

Es por tanto necesario por parte del paciente que alegue impericia por falta de un consentimiento informado:

> [E]stablecer que, de conformidad con los principios generales de la negligencia, que la falta de información adecuada fue la causa próxima del daño resultante.[15]

El caso en que nuestro Tribunal de Última Instancia resume la doctrina del consentimiento informado y establece su posición definitiva en relación al criterio que impera en Puerto Rico es *Sepúlveda de Arrieta v. Barreto Domínguez, supra.*

Este caso se trata de un médico que le realiza en 1979 a la demandante una blefaroplastía. En 1980 le fue diagnosticado por un oftalmólogo, que sufría de un ectoprión y demanda al Dr. Barreto alegando malapráctica profesional. El tribunal de instancia desestimó la demanda basándose en el testimonio del perito del demandado, que concluyó que las condiciones de ectropión y de *scleral show* son complicaciones reconocidas de una operación de blefaroplastía", que "dichas complicaciones son las más comunes" y que "pueden resultar de una blefaroplastía aún bajo las manos más diestras". Determinó que por la prueba presentada no le era posible concluir que el Dr. Barreto Domínguez hubiera extraído piel en exceso durante el procedimiento. Los demandantes instaron un recurso ante el Tribunal Supremo. Alegaron, entre otras cosas, que el consentimiento estuvo viciado ya que sólo se le había advertido de la posibilidad de hemorragia y hematoma. Manifestaron además, que de haber sabido que la blefaroplastía le iba a causar tantas molestias, jamás se hubiese sometido a ella.[16]

El Tribunal Supremo,[17] luego de analizar las tendencias que han sido adoptadas en las distintas jurisdicciones de los Estados Unidos, establece su posición al indicar que,[18] aunque lo ideal sería que el médico diera la más completa y total información sobre el tratamiento a ser administrado, las necesarias realidades de la práctica de la medicina imponen que la divulgación sea algo menos que completa. Establece el Tribunal que, en primer lugar, el conocimiento médico puede alcanzar niveles de complejidad que estarían fuera del alcance de una persona no diestra en ese campo, por lo que no podría ser comunicado efectivamente. En segundo lugar, el proceso de divulgar "toda" la información relacionada requeriría que el paciente fuera provisto del equivalente a una educación médica.

Confirmando lo indicado en la opinión concurrente de la Hon. Juez Naveira en *Ríos v. Mark, supra*, establece que, "luego de sopesar los criterios correspondientes, lo más apropiado es que adoptemos el criterio del profesional de la medicina, y no el del paciente razonable establecido en *Canterbury*", *supra.*

Luego de analizar los conceptos de causalidad imperantes en los países de tradición civilista, el Tribunal concluye que el análisis de causalidad en el sistema civilista no se hace desde el punto de vista de lo que habría hecho el paciente de haber tenido información adicional, sino de lo que le era exigible prever al médico como consecuencia normal de su omisión. Ya que en Puerto Rico rige la doctrina de la "causalidad adecuada" para determinar causalidad legal entre la acción u omisión negligente y el daño sufrido la cuestión a resolver consiste en determinar si la materialización del daño era de esperarse en el curso normal de los acontecimientos o si, por el contrario, queda fuera de ese posible cálculo.[19]

Revocando al tribunal de instancia, establece el Tribunal Supremo de Puerto Rico:[20]

> Aplicada al caso de autos, la cuestión a resolver consiste, entonces, en determinar si en el curso normal de los acontecimientos, le era exigible al Dr. Barreto Domínguez prever que la falta de la información debida llevaría a la paciente Sepúlveda de Arrieta a adoptar una decisión distinta de la que habría tomado de haber estado adecuadamente informada. En otras palabras, no es necesario determinar si ella, como paciente — subjetiva u objetivamente— habría consentido o no al acto médico propuesto, sino si le era exigible

[14] Ibíd. p. 665.
[15] Ibíd. p. 666.
[16] Ibíd. p. 826.
[17] Ibíd. p. 827.
[18] Ibíd. p. 829.
[19] Ibíd. p. 831.
[20] Ibíd. p. 831.

al Dr. Barreto Domínguez prever que la falta de información debida llevaría al paciente a exponerse a los riesgos no divulgados. Bajo este prisma, es obvio que en el curso normal de los acontecimientos, un cirujano debe prever que guardar silencio sobre un riesgo que, además de ser común en el procedimiento propuesto, produce un efecto desfigurante, a un paciente que desea someterse a una cirugía cosmética electiva, sin ningún valor terapéutico, llevaría muy probablemente al paciente a adoptar una decisión distinta de la que habría tomado de estar debidamente informado. No es necesario que el médico pudiera hacer esta determinación con certeza matemática. Basta que su negligencia fuera la que, en el curso normal de los acontecimientos, con mayor probabilidad pudiera ocasionar el daño, para que a éste le fuera exigible previsión y obligado a cumplir con el imperativo del Art. 1802.

Resulta, por lo tanto, innecesario recurrir a los criterios que ofrece la jurisprudencia de los Estados Unidos. La doctrina civilista de causalidad adecuada atemperada con la regla de la previsibilidad nos permite llegar a una solución justiciera.

Conclusión

El Tribunal Supremo adopta en *Sepúlveda de Arrieta, supra,* el criterio del profesional razonable,[21] pero requiriendo la divulgación de los riesgos materiales que sepa o deba saber que su paciente necesite para hacer una determinación de si someterse o no al tratamiento propuesto. La forma de determinar posteriormente qué información hubiera necesitado el demandante tendrá que hacerse tomando en consideración la totalidad de la circunstancias; esto es, el tipo de procedimiento, el propósito del mismo y a la posibilidad de complicaciones en balance con los beneficios esperados, entre otros.

Por tanto, y en vista de las normas legisladas y de la decisión del Tribunal en *Sepúlveda de Arrieta, supra,* el criterio que deben utilizar los tribunales es que la información que debe suministrar el médico al paciente antes de proceder a un tratamiento o procedimiento es aquella que los médicos de la comunidad acostumbran a dar a sus pacientes en igual circunstancias y que "llevaría muy probablemente al paciente, que entiende el contenido del consentimiento"[22] a acceder al procedimiento o tratamiento propuesto; y que, "según el curso normal de los acontecimientos, le [era] exigible ... [al médico] prever que la falta de [esa] información ... [llevaría al paciente] a adoptar una decisión distinta de la que habría tomado de estar debidamente informado".[23] Se le impone al médico a prever qué información necesita su paciente para poder estar en posición de tomar una decisión informada.

La mejor práctica es darle al paciente toda la información relacionada al procedimiento que incluya al menos una descripción en términos legos del procedimiento, todas las alternativas disponibles y que, a la luz de los modernos medios de comunicación y enseñanza, y conforme al estado de conocimiento de la ciencia y práctica prevalecientes en la medicina, satisface las exigencias generalmente reconocidas por la propia profesión médica.[24] Así mismo debe indicarle las posibles complicaciones, más aún aquellas que puedan poner en riesgo su vida o alguna función vital o que derrotarían los propósitos de la intervención, como ocurrió en *Sepúlveda de Arrieta, supra.*

Esta es la norma que deben tener presente los profesionales de la salud antes de proceder a administrar cualquier tipo de tratamiento o efectuar todo procedimiento a sus pacientes.

---

[21] Este mismo estándar es el propuesto en el Proyecto de Ley, Artículo 3, Sección 5, presentado a la Asamblea Legislativa y publicado en Prensa Médica, Publicación de la Asociación Médica de Puerto Rico de enero-mayo de 1995, p. 9.

[22] Del Reglamento 52.

[23] De *Sepúlveda de Arrieta, supra,* p. 831.

[24] *Rodríguez Crespo v. Hernández, supra,* p. 649.

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Reporte de Casos:

Electrocardiogram of the Month, Rosenbaum's Syndrome

*Charles D. Johnson, MD, FACC**

Case History

This 70-year-old female was admitted to Centro Cardiovascular de Puerto Rico with a history of mild symptoms of chest pains, dizziness, dyspnea, easy fatigability and bradycardia. There was no history of loss of consciousness. Her heart rate was 44 bpm. She subsequently was implanted with a permanent DDDR endocardial bipolar pacemaker.

Electrocardiograms (ECG): Figures 1 - 7.

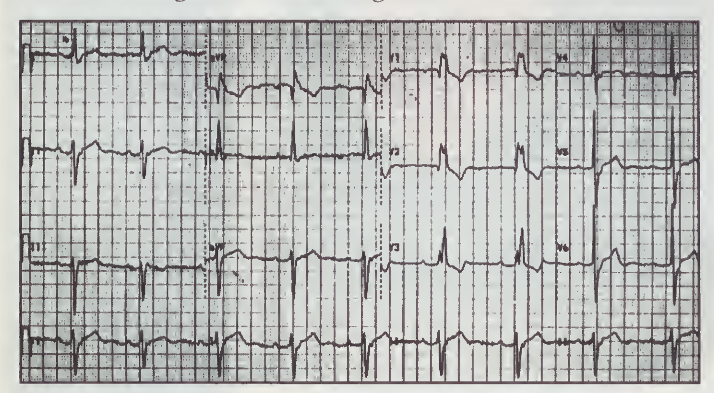


Figure 1. *7-15-99. Bifascicular block - RBBB + LAH + First degree AV block. HR 56 bpm. PR interval usually 0.24 sec. QRS 0.16, 0.18 sec. Axis -65 to -70 degrees. Q wave* V_{1-2}.

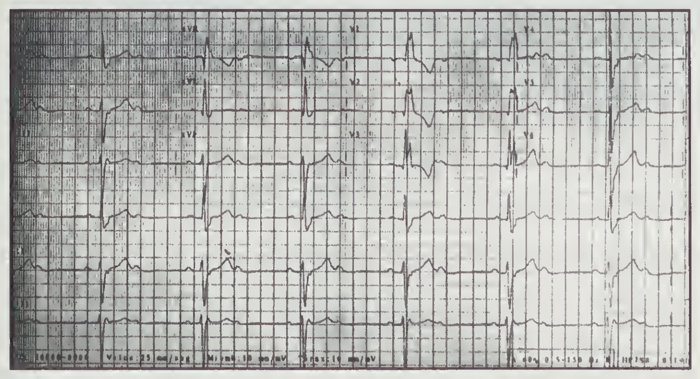


Figure 2. *7-21-99. RBBB + LAH + Second degree 2:1 AV block. 2:1 conduction in LPF. Positive VPP. LAE. P rate 77 bpm, QRS rate 39 bpm. PR 0.18-.20 sec. Axis - 85 degrees. q/Q wave* V_1-V_5.

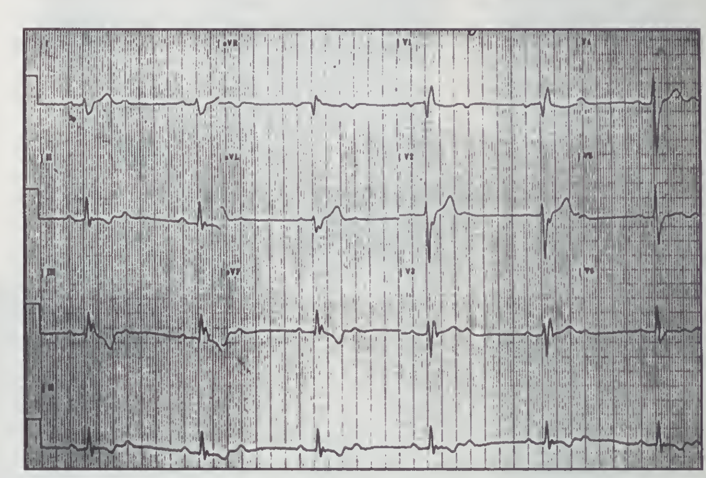


Figure 3. *7-20-99. RBBB + LPH + Second degree 2:1 AV block + First degree AV block. 2:1 conduction in LAF. LAE. P 75 bpm, QRS 37.5 bpm. PR usually 0.24 sec. QRS 0.17 sec. Axis + 125 degrees (RAD).*

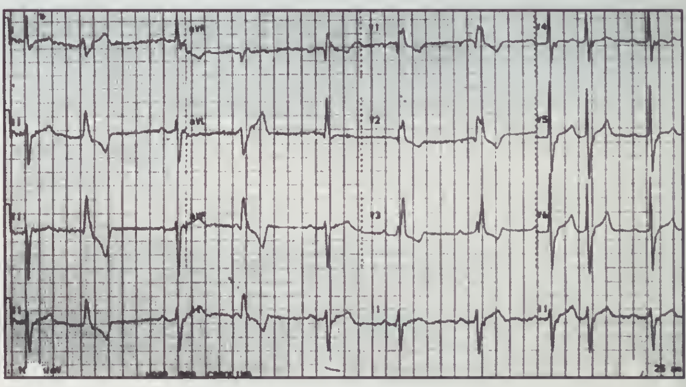


Figure 4. *Undated. RBBB + LAH + First degree AV block. HR 55, 59 bpm. PR 0.23-.24 sec. QRS 0.16 sec. Axis - 66 to - 75 degrees. Two FPB's, beats 2 and 4, with RAD-LPH morphology, may arise immediately distal to the block in the LAF. The penultimate beat may be an APB or JPB conducted with LAH. It may reflect SNC in the LPF.*

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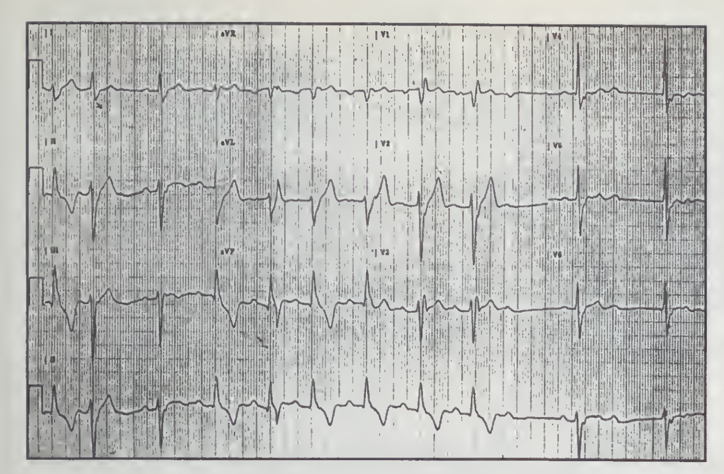


Figure 5. 7-17-99. RBBB + intermittent LAH and LPH (different QRS morphologies). LAE. LAH: HR 60 and 46.8 bpm, with block at the end; PR 0.21-.22 sec. LPH: HR 75-80 bpm, PR 0.25 sec. QRS 0.16-.17 sec. The second beat may be an APB or JPB conducted with LAH, reflecting SNC in the LPF, or a FPB originating just distal to the block in the LPF. At the right of the tracing during the LAH after the first nonconducted P wave, 3:2 Wenckebach conduction in the LPF may occur. The PR interval of the last QRS beat may be prolonged to 0.76 sec. This first nonconducted P wave may undergo CC or concealed penetration into the LAF, inducing LAH in the penultimate QRS beat; or the last two QRS beats with LAH morphology may be linked to the LPF, i.e. the LAF may be linked/subdued to the LPF. It likely reflects synchronous third degree block in both fascicles.

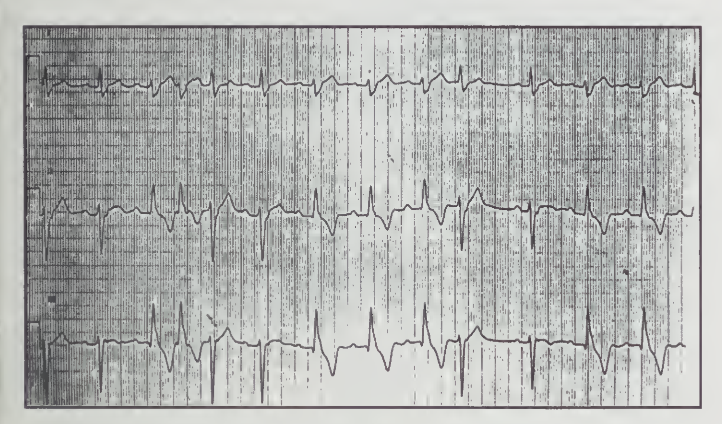


Figure 6. Undated. Leads I, II, III. RBBB + intermittent LAH and LPH. LAH: HR 73 bpm, PR 0.20-.23 sec; LPH: HR 71, 75 bpm. PR 0.23-.24 sec. The fourth QRS beat with LPH morphology may be a FPB originating in or near the LAF; it may induce retrograde CC/ penetration into the LAF causing LAH and into the AV node and His Bundle to prolong the PR interval, or SNC via the LPF may have caused linkage and subduing to the LAF resulting in LAH. The tenth beat with LAH morphology may be a FPB arising just distal to the block in the LPF.

Abbreviations: *AF-atrial fibrillation; AFl-atrial flutter; APB-atrial premature beat; AV-atrioventricular; CC-concealed conduction; FPB- fascicular premature beat; HR-heart rate; JPB-junctional premature beat; LAD-left axis deviation; LAE-left atrial enlargement; LAF-left anterior fascicle; LAH-left anterior hemiblock; LPF-left posterior fascicle; LPH-left posterior hemiblock; RAD-right axis deviation; RBBB-right bundle branch block; SNC-supernormal conduction; VPP- ventriculophasic phenomenon.*

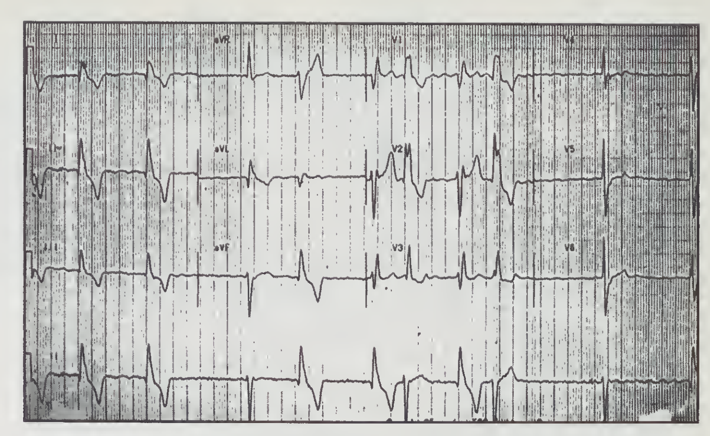


Figure 7. 7-14-99. IV Nitroglycerine. RBBB + intermittent LPH and LAH. AF or AF1. HR during LPH 62 and 57 bpm, axis + 70 degrees; HR during LAH 40 and 37.5 bpm, axis - 100 degrees. Q waves. The sixth and eighth beats with RBBB and LAH morphology may be FPB's arising immediately distal to the block in the LPF, or they might reflect SNC in the LPF with linkage to the LAF to produce LAH.

Diagnoses

Rosenbaum's Syndrome.

Trifascicular Block (TB)- intraventricular conduction abnormality. The syndrome of permanent complete right bundle branch block (RBBB) with intermittent, unstable blocks in the left anterior superior fascicle (LAF), left anterior hemiblock (LAH), and the left posterior inferior fascicle (LPF), left posterior hemiblock (LPH); and atrioventricular (AV), intraventricular conduction disturbances of first degree and 2:1 second degree (incomplete) AV blocks.

Discussion

This involves simultaneous conduction impairment / block in the three main terminal fascicles (disregarding the middle septal fascicle), the right bundle branch and the two (both) divisions of the left bundle branch.

This pattern has been regarded by some authors as bilateral bundle branch block. But other ECG authorities reserve the term "Bilateral Bundle Branch Block" for the presence of involvement, complete third degree block, of both the main bundle branches, presenting alternating or intermittent RBBB and left bundle branch block (LBBB) with a changing, different P-R interval. These hold that this is the only absolute evidence that both bundle branches are involved.

Bifascicular block is reflected by a combination of RBBB with LAH, or RBBB with LPH.

RBBB with either hemiblock, plus a first degree AV block (prolonged P-R interval) or a second degree AV block (dropped beats) has been suggested to be a manifestation of TB. However, the third site of block may not necessarily be in the remaining incompletely

blocked division, but at the level of the AV node or Bundle of His. A His Bundle recording would be necessary to distinguish this third site of partial block.

TB patterns are usually associated with Mobitz type II AV block.

Complete block in all three fascicles at the same time would lead to complete AV block.

A change in heart rate may bring about a change in the degree of block, i.e. rate-dependency TB. A few milliseconds difference may determine whether an impulse is normally conducted, entirely blocked or show concealed conduction.

Pathogenesis

Physiological mechanisms that may be underlying and playing a role in this case of TB are listed in Table I.

TABLE 1.
Physiological Mechanisms In Trifascicular Block

1. Third degree block in the right bundle branch.
2. First degree and second degree (2:1, etc Mobitz II) blocks in the two fascicles of the left bundle branch, and third degree.
3. Heart rate changes - duration of diastolic intervals; duration of recovery to changes in rate.
4. Refractoriness. Fascicular refractoriness. Cycle length influence on refractoriness.
5. Crossover of recovery curves.
6. Supernormality, in the anterior and posterior divisions (intraventricular) of the left bundle expressed as early captures.
7. Spontaneous diastolic depolarization- phase 4 depolarization.
8. Concealed Conduction - concealed bundle branch and fascicular penetration in the two fascicles/divisions.
9. Linking - retrograde activation of the two fascicles by an impulse coming down the opposite fascicle; implies that conduction in one fascicle is dependent on conduction in the other fascicle.
10. Gap phenomena, Type II.
11. Autonomic, hemodynamic and electrolyte influences.
12. Geometry, anatomy and pathology of the fascicles.

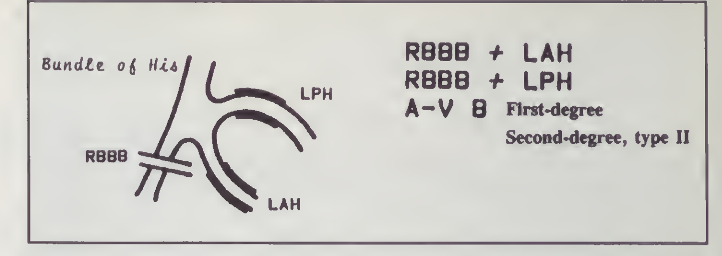


Figure 8. The transverse bars indicate that conduction is permanently interrupted. The lengthwise bars indicate unstable or intermittent conduction.

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EDITORIAL

Rosa Pérez Perdomo, MD, PhD
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(Editorialista Invitado)

La información en el sector Salud

La importancia de la información en salud pública es un hecho ampliamente reconocido. Disponer de datos confiables y válidos es esencial para entender mejor los determinantes básicos de la salud (Evans et al). Por ejemplo, la Organización Mundial de la Salud (OMS) ha establecido que "el camino que conduce a la salud para todos pasa por la información". Sin embargo, a pesar de que está ampliamente aceptado la importancia de tener datos confiables esta suele ser una tarea difícil y de un alto costo. Por otro lado, la prestación y gestión de atención de salud en cualquiera de sus modalidades es una tarea compleja que dependerá en gran medida de la información en la que se sustenta. El reto radica en recopilar, analizar y diseminar datos

(Continúa en la pág. 58)

de calidad si se pretende tener una prestación de servicios exitosa.
La mayoría de los países tienen diferentes tipos de información en salud que recopilan sistemáticamente, en particular, las llamadas estadísticas vitales que incluyen principalmente información relacionada con nacimientos y mortalidad. Algunos países tienen sistemas de vigilancia epidemiológica de enfermedades específicas tales como cáncer, diabetes, dengue y VIH/SIDA entre otros. Además, en muchos países se recopila algún tipo de información sobre prestación de servicios, el costo de los mismos y satisfacción de los usuarios. Sin embargo, a pesar de que la mayoría de los países suelen tener algún sistema de recopilar información en salud existe un gran nivel de desconfianza en relación a la calidad de los mismos. Entre un gran número de problemas relacionados con esta información se pueden mencionar el subreporte, información incompleta, falta de automatización, falta de coordinación, falta de cooperación de los proveedores, falta de agilidad en la presentación y difusión de los datos y posiblemente el más importante, la poca demanda de la información entre los encargados de formular la política pública así como entre los administradores de programas, que parecen no estar consciente de la importancia estratégica y la utilidad práctica de la información en salud para la planificación y ofrecimiento de servicios de salud (OPS, 1998).
Con mucha frecuencia escuchamos en nuestro medio hablar de que determinada enfermedad es importante en Puerto Rico, pero se desconoce su incidencia y prevalencia y menos aún su distribución por factores tan básicos como la edad, el sexo, o el area geográfica. Ante esta situación se suelen citar datos de otros países asumiendo que esta enfermedad se comporta de igual forma en Puerto Rico, lo que no siempre es correcto. Por otro lado, el tener datos relacionados con una condición es de vital importancia para un investigador que desea obtener financiamiento para un proyecto donde tiene que justificar el mismo porque la condición se considera altamente prevalente en nuestro medio. En fín, se tiene que crear conciencia dentro de la clase médica y otros profesionales de la salud de la importancia de la recopilación, análisis y utilización de la información en salud.
Iniciemos un esfuerzo coordinado para completar adecuadamente los expedientes médicos que suelen ser en su gran mayoría una fuente primaria para la obtención de datos sobre salud. Les exhortamos a que participen activamente en los esfuerzos coordinados para proveer información a aquellos sistemas de vigilancia o registros que ya existen en Puerto Rico, tales como el registro de cáncer, SIDA y diabetes.
La información recopilada redundará en una práctica médica mejor dirigida hacia las necesidades de nuestra población. De igual forma, el nuevo escenario de prestación de servicios de salud hace que el médico asuma el riesgo financiero de mantener una armonía entre el cuidado de sus pacientes y la utilización de recursos. Esto hace vital la disponibilidad y utilización de la información para manejar sus pacientes de forma costo-efectiva.

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Estudios Originales:

Excellent Response to Interferon Therapy in a Patient with Hypereosinophilic Syndrome and Elevated Serum Immunoglobulin E Levels

Luis Acaba MD, FACP, Amarylis Mangual MD, and Enrique Vélez García MD, FACP

Introduction

The hypereosinophilic syndrome (HES) is an uncommon heterogeneous disorder characterized by sustained eosinophilia of greater than 1,500 eosinophils x 10^9/L with evidence of end-organ damage. Without any specific diagnostic markers, a comprehensive evaluation is necessary to differentiate the HES from benign disorders such as parasitic, allergic, or other recognized reactive causes of eosinophilia. The HES must also be distinguished from malignant eosinophilic leukemia, which is usually characterized by increased numbers of immature blast cells and cytogenetic abnormalities typically seen in acute nonlymphoblastic leukemia. Several factors have been shown to influence the prognosis in the HES. Extremely high leukocyte counts and cardiac damage are associated with an adverse prognosis (1). Various immunologic abnormalities have been reported in the HES, with elevated serum immunoglobulin E (IgE) levels one of the most commonly observed. Historically, this subgroup of patients is associated with an excellent prognosis (2, 3). Since many patients present with a mild chronic disorder, therapy of the HES is directed at controlling the organ damage and not necessarily the eosinophilia. The optimal therapy of HES is unknown and mostly empirical. Varied responses to steroids, hydroxyurea, and cyclosporin A have been reported (4-6). Allogeneic bone marrow transplantation has been performed in a few select patients (7). Recently, several reports have described the use of alpha-interferon in this disorder. Responses have been seen in patients resistant to conventional treatment (4, 8).

We describe a patient with severe HES and elevated IgE levels refractory to alkylating chemotherapy, steroids, and hydroxyurea. A dramatic and durable response was obtained with the use of interferon therapy.

Case Report

The patient is a 31 year-old male with a seven-year history of allergic rhinitis and urticaria, occasionally treated with oral antihistamines. He worked as a part-time tour guide at a subterranean cavern located in Camuy, Puerto Rico. He developed worsening of his allergic symptoms for which he was evaluated by an allergist. An allergy panel was performed and the patient was reactive to multiple common environmental allergens. The patient was administered "desensitization" injections containing ambient allergens for a period over five months. Complete blood counts (CBC) performed during this period revealed 10,000-15,000 x 10^9/L total white blood cells (WBC) with a normal differential.

The patient subsequently developed progressive generalized malaise, a 20 pound weight loss and marked muscular and bone aches over a period of two months. He was admitted to another hospital and the CBC revealed 200,000 WBC, the differential revealing 95% eosinophils, 2% bands, 2% monocytes, and 1% myelocytes. He was treated with a pulse of oral mephalan chemotherapy, but persisted with the elevated WBC

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count. He was transferred to our institution, complaining of generalized pruritus, chills, night sweats, persistent dry cough and exertional dyspnea. Physical examination revealed decreased breath sounds associated with ronchi in the base of the left lung. The skin revealed a generalized eythematous macular skin rash with scattered areas of flaky, scaling epidermis. There were no cardiac murmurs or gallops. The liver span was eight centimeters and the splenic tip was palpable. The neurological exam was normal and there was no lymphadenopathy. CBC revealed a leukocyte count of 259,000 x 10^9/L, the differential revealing 93% eosinophils, 3% neutrophils, 3% lymphocytes, and 1 % monocytes. The hemoglobin was 12.0 g/dL with normocytic indices and the platelet count was 350 x 10^9/L. The serum chemistry values and liver function tests revealed an elevated lactate dehydrogenase of 535 U/L, alanine aminotransferase of 170 U/L, alkaline phosphatase of 142 U/L, and GGT of 195 U/L. The aspartine aminotransferase and CPK were within the normal range. The serum vitamin B,2 level was elevated at 2,063 pq/ml (normal value: 200-800 pq/ml). The Westergreen sedimentation rate was within the normal range. The leucocyte alkaline phosphatase (LAP) score was decreased at 5 (normal value: 11-95). Serologic tests for HIV, hepatitis A, B, and C, VDRL and antinuclear antibodies (ANA) were negative. Various stool examinations were negative for ova and parasites. Serum immunoglobulin levels revealed normal levels of IgG, IgA, and IgM. The serum IgE level was elevated at 1,127 U/ml (normal value: 10-180 U/ml). Bone marrow aspirate and biopsy revealed a hypercellular marrow, with hyperplasia of mature eosinophils. The blast count in the aspirate was less than 1 %. Cytogenetic analysis of the bone marrow was normal. Immunophenotyping revealed expression of the mature myeloid markers CD 13 and CD 14. Cytochemical studies revealed reactivity of the cells with Sudan black and PAS, consistent with the observed eosinophils. The chest x-ray revealed a minimal left lower base infiltrate. An echocardiogram revealed a left ventricular ejection fraction of 60% with minimal left atrial enlargement, without any valvular abnormalities or effusions. Treatment with oral hydroxyurea and intravenous steroids was begun. Six days later there was a decrease in the WBC's to 60,000 x 10^9/L, but the percentage of eosinophils remained at 90% and the hemoglobin and platelet count decreased to 10 g/dL and 68 x 10^9/L, respectively. The skin rash and the generalized pruritus increased. The dyspnea worsened, accompanied by a severe right pleuritic chest pain. The arterial blood gasses at room air revealed relative hypoxemia (PO_2 = 73 mmHg) for which oxygen supplementation was required. He developed severe bilateral knee pain and sharply marginated painful "aphthous-type" oral ulcers in the upper palate and a left foot ulcer. Bilateral knee radiography did not reveal any abnormality and a bone scan revealed only a minimal increase in knee uptake. On the tenth day of admission the CBC revealed a leukocyte count of 10,000 x 10^9/L, the differential revealing over 90% eosinophils. The hemoglobin was 5.7 g/dL and the platelet count was 8,000 x 10^9/L, for which multiple pRBC's and platelet transfusions were administered. The patient remained on steroids and the hydroxyurea was discontinued. Despite the decrease in leukocytes, the oral and foot ulcers progressed and the joint pains became more intense. The follow-up chest x-ray revealed multiple bilateral pneumatoceles associated with a hydro-pneumothorax in the right lung base, confirmed by chest computerized tomography. At this time interferon-alpha (IFN alpha-2b, Intron A, Schering Plough), 3 million units subcutaneous three times a week was begun. After the fourth dose, the differential revealed an eosinophil percentage of less than 1%. During the following few days the skin rash faded and the ulcerated oral and foot lesions healed. The spleen was no longer palpable. His dyspnea as well as the pleuritic chest pain disappeared. His PO_2 returned to normal and the joint pains resolved. Steroid tapering was begun. He was discharged 12 days later with a CBC revealing a leukocyte count of 6,000 x 1 09/L, the differential revealing 54% neutrophils, 29% lymphocytes, 15% monocytes and 2% eosinophils. The hemoglobin was 13.6 g/dL and the platelet count was 213 x 10^9/L. The liver function tests returned to normal and his serum IgE level decreased to 116 IU/ml. The patient continued on interferon therapy for a total of three years without any further complications or significant change in the CBC. A repeat bone marrow aspiration and biopsy revealed no morphologic abnormality. Five years after the onset of HES he remains well and is fully active without any medication. His CBC remains essentially unchanged, with a differential revealing less than 2% eosinophils.

Discussion

The natural history of the HES is highly variable. The hematologic and clinical manifestations are heterogeneous between patients. Further rendering the diagnosis difficult is the absence of a specific test distinguishing between a malignant from a nonmalignant

process in the HES. This distinction would be of the utmost importance, as it would determine the need for a specific therapy. Since an elevated eosinophil count in itself is not deleterious, therapeutic intervention would only be required with evidence of organ involvement. Recently polymerase chain reaction (PCR) analysis employing X chromosome inactivation has been shown to distinguish reactive from clonal eosinophilia in female patients presenting with HES (9). Further refinements of this method may allow an accurate diagnosis, with earlier therapy of the malignant eosinophils. The pathogenesis of the HES is mainly a result of the release of specific granules and cytokines released by the activated eosinophil. These substances exert toxicity on the host cells and further proliferation and activation of eosinophils (4).

The patient presented with multiple manifestations clearly suggestive of a malignant disorder. The extremely elevated eosinophil counts, the clinical involvement of the skin and mucous membranes, lungs, joints, and splenomegaly are consistent with a myeloproliferative disorder. Besides the splenomegaly the patient presented with a decreased LAP score and elevated vitamin B_{12} levels, which are characteristic of chronic myelogenous leukemia (CML). Splenomegaly is seen in 40% of patients with HES and abnormalities of vitamin B_{12} and LAP score are not uncommon (1). Furthermore, elevated eosinophil counts are not characteristic of CML and it is usually associated with the Philadelphia chromosome, which was not detected in the patient.

The patient presented with a markedly elevated IgE serum level, which is seen in 38% of patients with HES. It has been suggested that in this group of patients the eosinophilia is a result of an IgE-mediated hypersensitivity response to an unknown antigen (3). The hypereosinophilia the result of a dysregulated proliferation of a clonal population of eosinophils stimulated by the IgE (9). The fact that the patient worked in a cave, exposed to bat droppings, fungi and other multiple antigens raises the possibility of this being a possible precipitating factor. The possible antigenic role of the "desensitizing" injections also has to be considered. In previous reports patients presenting with increased IgE levels have had an excellent prognosis, not requiring any therapy or responding promptly to steroids (2, 3). The patient not only required treatment but was also refractory to steroid therapy. Despite the steroids and a decrease in the absolute eosinophil count with hydroxyurea, symptoms progressed. This not only reveals the heterogeneity of the HES but that possibly other variables, such as the total eosinophil count and organ involvement at presentation are more significant prognostic factors.

The patient's clinical course improved dramatically once interferon-alpha therapy was begun. Interferon-alpha is one of the several naturally occurring proteins produced in response to stimulating antigens. It has diverse biological effects, including modulation of the immune system, regulation of cytokine expression, and inhibition of proliferation. It has been used extensively for the treatment of CML, where it has been shown to produce significant hematological and cytogenetic responses in the majority of patients (10).

Several reports have demonstrated its efficacy in the HES. In most of these reports the patients were resistant to conventional therapy and almost all had a beneficial effect to alpha-interferon (2, 4, 8, 11, 12). The mechanism of action of interferon in the HES is unknown. Human eosinophils have been found to express a functional receptor for alpha-interferon. In addition, alpha-interferon has been shown to inhibit the release of eosinophil granule proteins, a possible cause of the organ damage in the HES (13). However, the beneficial effect seen with alpha-interferon in distinct hematologic malignancies suggests a nonspecific common regulatory pathway, such as immunomodulation (10).

In summary, the patient presented with an aggressive form of HES refractory to conventional therapy. Despite the elevated IgE level at presentation, suggestive of a good prognosis, he clearly had an aggressive variant of the HES. This demonstrates the diversity of the HES and the need for a reliable scoring system to classify patients into prognostic groups. At present, for patients presenting with complicated HES, we believe that therapy with alpha-interferon should be started soon after the initial diagnosis is confirmed.

Summary

The hypereosinophilic syndrome (HES) is a heterogeneous disease characterized by sustained eosinophilia for a period of at least six months with evidence of organ involvement. Its manifestations range from a benign disorder not requiring any therapy to an aggressive, malignant variety refractory to common treatments. Diverse therapies have been used, including steroids, hydroxyurea, and chemotherapy, with variable responses. Recently alpha-interferon therapy has been shown effective in this disorder. Of the various prognostic factors, elevated serum immunoglobulin E (IgE) levels is

considered among the most favorable, with most patients presenting with a "benign" disorder, not requiring therapy. We describe a patient presenting with an aggressive variant of HES despite having elevated IgE levels. The patient had a dramatic and lasting response to alpha-interferon.

Resumen

El síndrome hipereosinofílico (SHE) es un desorden heterogéneo que se caracteriza por eosinofilia persistente por un período de seis meses con evidencia de daño de órgano. Sus manifestaciones varían desde una enfermedad benigna que no requiere tratamiento hasta una enfermedad maligna que no responde a terapias convencionales. Se han utilizados varios tratamientos, incluyendo esteroides, hydroxyurea y quimioterapia, con resultados variables. Recientemente, se ha demostrado la efectividad de interferon-alfa en este desorden. De los varios factores de pronóstico, el nivel elevado de la inmunoglobulina E (IgE) se considera uno de los más favorables, ya que la mayoría de estos pacientes no requiere tratamiento. Describimos un paciente que presentó una variante agresiva del SHE, a pesar de tener niveles elevados de IgE. El paciente obtuvo una respuesta dramática y duradera con tratamiento de interferon-alfa.

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Estudios Originales:

Profile of Internet Users: Survey of the Surgical Section of the AAP

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Abstract

Background: Communication through electronic networks is becoming a most useful resource of health care providers.

Purpose: Establish the demographic and professional profile and identify the internet service provider of members of the Surgery Section of the American Academy of Pediatrics (AAP).

Materials: A short survey questionnaire including variables of age, gender, years of experience, type of practice and internet service provider was mailed to all members of the Surgical Section of the AAP. Two-hundred and six responses of 588 (35%) were received and analyzed.

Results: Mean age of the group was 52 years of which 88% were male and 12% female (7.5:1). The group had an average of eighteen years of practice; 185 members (90%) have access to Internet and 188 (92%) use it mainly for e-mailing from either home (25%), hospital/office setting (30%) or both (42%). Twenty-three percent of member were willing to receive section news and correspondence by electronic means, by print-mail 34% and both 44%. Overall type of practice was private 21%, University 54% or combined 23%. No access to internet means an older member (57 yrs, p = 0.02) sharing solo (private) practice (p = 0.006). Two-third of internet service providers were university-based (-edu) or hospital organizations (-org) with a younger age group (48 yrs, p = 0.000001).

Conclusions: E-mailing is becoming the preferred method of communication among many members of the Section of Surgery of the AAP. Net accessibility through University or Children Hospital servers account for the high number of young members in this practice setting.

Key words: internet, surgery section, American Academy of Pediatrics

Internet, the largest network of connected computers, is producing a profound influence in the delivery of health care systems. Basic resources of this technology are electronic mailing (E-mailing), discussion groups (news groups and list servers), file transfer, and its crowning glory, the World Wide Web.[1] It has been suggested that pediatric surgeons use this net-work mainly as a communication tool.

The aim of this report is establishing the demographic and professional profile as well as the internet service provider of physician members of the Surgery Section of the American Academy of Pediatrics (AAP).

Materials

A short survey questionnaire that included variables of age, gender, years of experience after training, type of practice and internet service provider was mailed in 1997 to all members of the Surgical Section of the AAP after approval from the executive committee. Two-hundred and six replies from 588 members (35% response rate) were received and analyzed.

Analysis of the data was done using EPI-INFO statistical package (CDC, Atlanta). A probability less than 0.05 was considered statistically significant where applicable. All results were expressed as mean +/- standard deviation.

Results

The mean age of the group was 52 years; 88% were males and 12% female (7.5:1). This figure corresponds similarly to the actual gender distribution within the surgery section of the AAP. A fair distribution in years of practice into those less than ten years (28%), between 10-20 (33%) and more than twenty years (39%) was found. With an average of eighteen years of practice, 188 pediatric surgeons (92%) have access to Internet and 185 (90%) use it mainly for electronic mailing from either home

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(25%), hospital/office setting (30%) or both (42%).

Regarding the issue of E-mail utility, members willing to receive section news and correspondence by electronic means were 23%, by printed-mail 34% and by both means 44%. Older members insisted on receiving printed instead of electronic material (age = 55 y/o, p = 0.002). 82% of the group was willing to include their e-mail address within the AAP web pages. Older members would not include the electronic address (age 57 y/o, p = 0.001).

Overall the type of practice was private 21%, University 54% or combined 23%. No access to internet portrays an older member (57 yrs; p = 0.02) sharing solo (private) practice (p = 0.006). Two-third of internet service providers is university-based (-edu) or hospital organizations (-org) within a younger age group (48 yrs, p = 0.000001).

Discussion

A substantial number of members of the surgery section of the AAP have internet access. Main use is electronic communication along with list server discussion groups. The swift, reliable and economical method of access along with the pressure exerted by a younger population of physicians have forced health carers to take hands-on computer-based technology. List server discussion creates a perfect environment to consult colleagues on a clinical problem, send draft of a paper for peer revision, read journals without paying subscription rates, maintain your continuing medical education credits, and retrieve anything the same day that it is published online.[2] It will become an essential tool in medical research, teaching medical students, clinical practice, postgraduate studies, and continuing medical education. It is a constant forum for exchange of ideas, difficult cases, consensus on management, and development of our specialty.

By re-architecturing the workplace pediatric surgeons have anticipated the informatics capabilities of this computer-based technology creating a new vision of work and organization in such areas as service, teaching and research. Our survey demonstrates that there is a rapid growth of computer based electronic communication and the new generation of pediatric surgeons feel comfortable with the electronic transfer of information, a trend in health care already foreseen by others.[3] Electronic communication may create a strong alliance of pediatric surgeons around the world.[4]

Internet service providers (ISP) among members are either private or universities based. The service provider will give access to the Net using a local or toll-free telephone number. Some include web space with the monthly rate offer. A university-based ISP usually provides service for a nominal or none rate. Electronic addresses of such users usually end in the suffix -edu. Most physicians with internet access have it through academic affiliation.[5]

Resumen

Las comunicaciones electrónicas son el recurso de mayor utilidad para los proveedores de salud. El propósito de este estudio consistía en establecer las características demográficas y profesionales e identificar proveedores de servicios de internet que utilizan los miembros de la Sección de Cirugia de la Academia Americana de Pediatría. Se envío un cuestionario a todos sus miembros que incluía variables como edad, sexo, años como cirujano pediátrico, tipo de practica y proveedor de servicio de internet. Se recibieron y analizaron 206 respuestas (35%) de 588 miembros. La edad promedio del grupo fue de 52 años; 88% eran varones y 12% hembras (proporción 7.5 a 1). Con un promedio de 18 años en práctica quirúrgica, 185 miembros (90%) tienen acceso a Internet y 188 (92%) utiliza correo electrónico desde su casa (25%), el hospital/clínica (30%) o en ambos sitios (42%). 23% de los miembros desean recibir su correspondencia y noticias de la sección quirúrgica por medios electrónicos, por correo postal 34% y por ambos medios 44%. En general, el tipo de práctica es privada en 21% del grupo, asociada a una Universidad 54% o combinada en 23%. Miembros mayores (edad 57 años, p = 0.02) en práctica privada sola (p = 0.006) no tenían acceso a Internet. Dos-terceras partes de los proveedores de Internet eran de la Universidad (-edu) o del Hospital en que trabajaban (-org) siendo un grupo de personas mas jóvenes (48 años, p = 0.00001). El correo electrónico se ha ido convirtiendo en el método preferido de comunicación entre muchos miembros de la Sección de Cirugia de la Academia Americana de Pediatría. El acceso a través de las Universidad o los Hospitales Pediátricos es responsable de este alto número de miembros conectados.

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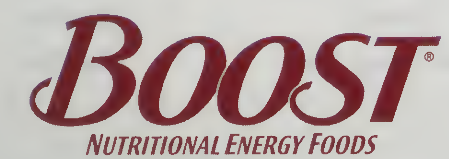
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Artículos de Revisión:

Treatment of Primary Cardiac Malignancies with Orthotopic Heart Transplantation

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Rosa M. Cintrón-Maldonado, M.D.; Thomas J. Forbes, M.D.

Abstract

Objective: Heart transplantation has become available as a possible treatment for patients with malignancies. Primary cardiac malignant tumors are extremely rare but several patients have been treated with this modality. Whether survival is improved over the direct removal of tumor or heart transplantation is not known. We compiled data regarding malignant primary heart tumors that have been treated at various transplant centers in order to determine if early diagnosis and treatment with cardiac transplantation has resulted in an improved mortality.

Methods: A total of 173 questionnaires were sent to the heart transplant centers across the United States and Canada inquiring about those patients who were found to have a primary cardiac malignant tumor and who underwent heart transplantation. Cases reported in the literature, which had undergone transplantation, were also reviewed by a search in MEDLINE.

Results: Twenty-four cases were collected. The overall survival time was from 1 month to 66 months. The actuarial survival was 54% at 12 months, 45% at 24 months and 35% at 36, 48 and 60 months respectively. Metastases were present in 10 out of the 14 deceased patients, possibly being one of the major factors affecting survival. Only 1 living patient developed metastases.

Conclusion: Survival rates of patients with primary cardiac malignancies treated with resection, radiation, chemotherapy, or a combination of them (conventional therapy) versus heart transplantation are similar. Early diagnosis and resection are the most important factors for a better outcome, however these factors will not guarantee success since the presence or development of metastasis is a major contributor to death in both groups of patients.

Introduction

Primary cardiac malignant tumors are rare and frequently lethal, however, early recognition may lead to treatment, which in some instances might lead to a cure. The clinical outcome is dependent upon many factors including the type of tumor and its early recognition. The purpose of this study is to compile data of all malignant primary heart tumors that have been treated at transplant centers in order to determine if treatment with cardiac transplantation has resulted in an improved mortality.

Methods

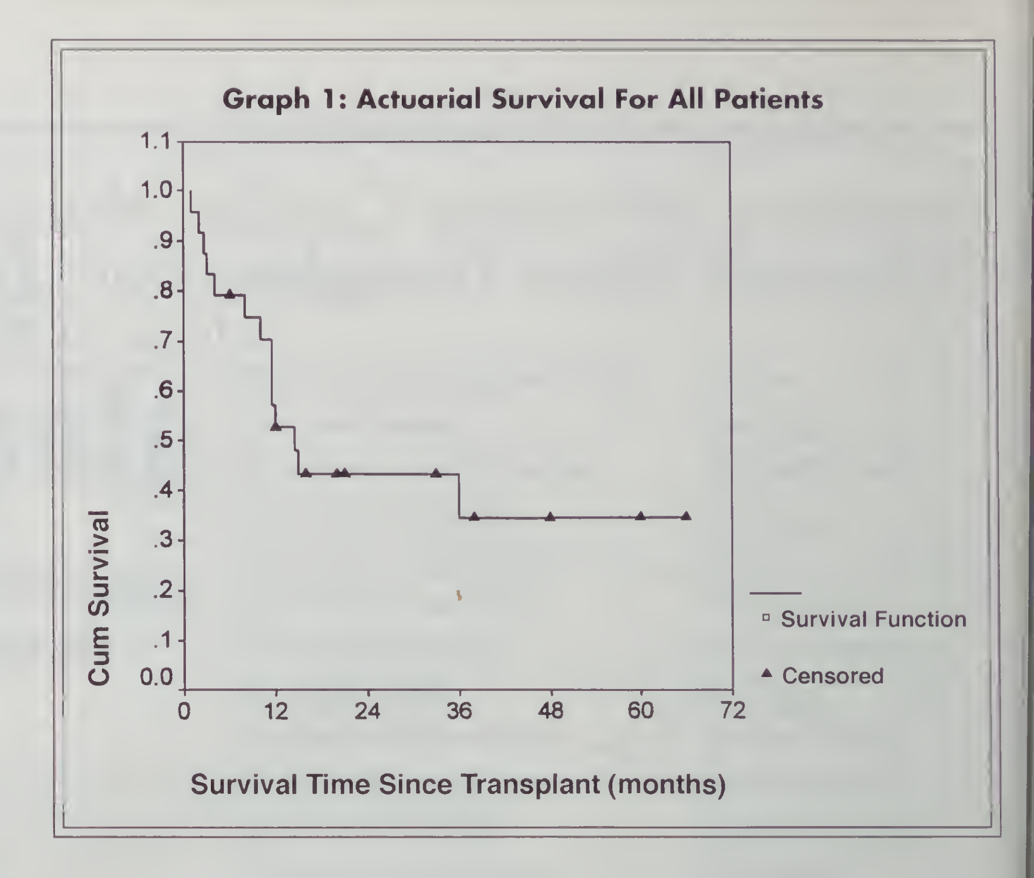
Major transplant centers in the United States and Canada were surveyed for those patients who were found to have a primary cardiac malignant tumor and who underwent cardiac transplantation. Information on survival times and the presence of metastases was requested to determine if this mode of treatment was likely to be successful. Personal, telephonic and electronic mail communications were used to gather data.
Cases reported in the literature which had undergone transplantation were also reviewed by a search in MEDLINE.
A total of 168 letters were sent to the transplant centers in the United States and 5 letters were sent to centers in Canada. Calculations were derived from data only on those patients for whom information was available. Actuarial survival was obtained by the Kaplan-Meier method.

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Results

The response rate for the 173 letters sent was 75.5 %. Twenty-four patients with primary cardiac malignancies were transplanted, (Tables 1 and 2) and all were reported as having no known metastases prior to the transplant. Of these 24 cases who underwent heart transplantation 7 had angiosarcomas, 3 lymphomas, 2 leiomyosarcomas, 2 osteosarcomas, 2 histosarcomas, 2 undifferentiated sarcomas, 2 fibroma/sarcoma, and 4 had another miscellaneous histologic type of tumor. Two cases were reported as having malignant potential, thus included in this study.



The mean age at the time of diagnosis was 34 years old, with a range of 7.5 to 64 years of age. This study included 13 males (54%) and 11 females (46%). The overall median survival time was 12 months from the time of transplant, with a range of 1 month to 66 months. Ten of these patients were alive and 14 were deceased at the time of this report. Follow up information was unavailable for one patient. The actuarial survival was 54% (13) at 12 months, 45% (5) at 24 months, 35% at 36, 48 and 60 months respectively (2 per year). (Graph1) The median survival time for the group living (Table 1) is 27 months, with a range of 6 to 66 months.

For the deceased group, (Table 2) the median survival time was 10.75 months with a range of 1 to 36 months. Ten of the 14 who died had documented metastases. Only 1 of the surviving patients had metastasis. Information about metastasis was not

Table 1: Patients Treated with Heart Transplantation- ALIVE

Type of Tumor	Age/Sex	Locotion of Tumor	Woiting Time for tronsplont	Tumor Free Morgins	Chemo	Rodio	Survivol Time Since Tronsplont (months)	Metostosis/ Locotion
Angiosorcomo (16)	42/F	LA	10 mo	Yes	Yes	Yes	6	No
Neuroectodermol (17)	63/M	Septum RV	5 mo	-	No	No	12	No
Myxosorcomo (16)	42/F	LA	27 mo	-	Yes	No	16	No
Sorcomo (18)	—/M	-	-	-	-	-	20	-
B cell lymphomo	8/M	-	-	-	-	-	21	No
Angiosorcomo (19)	34/M	-	-	-	Yes	Yes	33	No
Fibromo* (20)	49/F	LA	21 mo	Yes	No	-	38	No
Fibrosorcomo (21,22)	31/F	Pericordium RV, LV	3 doys	Yes	Yes	-	48	Lung
Pheocromocytomo* (20)	27/F	Epicordium LA, LV	6 mo	Yes	No	-	60	No
Neurofibrosorcomo (23)	43/F	RV	-	-	No	No	66	No

KEY
* = Considered malignant
\- = No Information
M = Male
F = Female
LA = Left atrium
RA = Right Atrium
RV = Right Ventricle
LV = Left Ventricle

available in 2 patients. Commonly the chambers involved were the atria with 15 (62.5%) tumors, and the ventricles, with 11 (46%). Chemotherapy was given to 12 patients: 4 alive (33%), and 8 of the dead group (67%). Only 2 patients were known to have received radiotherapy. Tumor-free margins were reported in 6 (25%) patients only. Of the 6 patients who had tumor-free margins the 2 who did not receive chemotherapy or radiotherapy had longer survival times.

We also analyzed several published papers in which diagnosis, survival, and conventional treatment (resection, chemotherapy, radiotherapy, or combination) were discussed (Table 3). A total of 104 tumors were found in 54 males and 50 females. The most common types were 21 rhabdomyosarcomas, 20 angiosarcomas, 11 fibrous neoplasms, 10 myxosarcomas, and 10 histosarcomas. The most common chambers of appearance in this group of patients were the atria with 82 (79%) tumors in total. Surgical intervention or biopsy was carried out in 86 patients. Complete excision was reported in only 21 of the 86 cases. Chemotherapy was administered to 52 patients and radiotherapy to 15 patients. Approximately 50 of the patients treated with chemotherapy died within 24 months. The survival rates were 32% at 12 months, 23% at 24 months, and 9% at 36 months. At least 5 (5%) patients survived more than 48 months.

Discussion

McAllister and Fenoglio (1) found an incidence of primary tumors of the heart to range between 0.0017% and 0.28% based on autopsy studies. Reynen, et al, (2) analyzed autopsy studies reported in the literature and found an incidence of 0.02% corresponding to 200 tumors in 1 million autopsies; of these tumors, approximately 25% were malignant.

Sarcomas are the largest group of primary cardiac malignant neoplasms.(3-5) Of these sarcomas, angiosarcomas are the most common histologic type which are reported to occur more commonly in males than females (4) and are often found in the right atrium, frequently extending to the pericardium, vena cava, or tricuspid valve. Metastases are common and often widespread. Other neoplasms include rhabdomyosarcomas, osteosarcomas, fibrosarcomas, lymphomas and miscellaneous histologic types. (1, 6) The signs and symptoms of these tumors at presentation are generalized and non-specific.

Although the incidence of primary cardiac malignant tumors is very

Table 2: Patients Treated with Heart Transplantation- DEAD

Type of Tumor	Age/Sex	Location of Tumor	Waiting Time for transplant	Tumor Free Margins	Chemo	Radio	Survival Time Since Transplant (months)	Metastasis/ Location
Burkitts lymphoma	18/M	-	-	-	Yes	No	1	No
Angiosarcoma (24)	29/F	RA	8 mo	Yes	Yes	No	2	Lungs, Pleura
Sarcoma (16)	64/M	RV, LV	2 mo	-	No	-	2.6	-
Synovial sarcoma (15)	31/F	RA, LA, LV	2 mo	-	No	No	3	Mediastinum, left hemithorax
Histocytofibroma (25)	35/M	LA	25 mo	-	Yes	No	4	Inferior Vena Cava
Angiosarcoma (14)	31/M	RA	2 mo	Yes	Yes	No	8	Brain, Bone, Liver
Angiosarcoma (14)	32/M	RA	-	-	Yes	No	10	Brain
Leiomyosarcoma	7.5/M	RA	28 mo	-	-	-	11.5	No
Osteosarcoma	28/F	LA	1 mo	No	No	No	11.5	Brain, Heart
Leiomyosarcoma	9/M	RV	-	-	-	-	11.5	No
Angiosarcoma (26)	27/F	RA	8 mo	-	Yes	No	12	Lungs
Angiosarcoma (20,27-29)	13/M	RA,Septum	-	No	Yes	-	14.5	Mediastinum
Lymphoma (30)	57/F	RA, RV, LV	9 days	No	Yes	-	15	Bone Marrow
Histosarcoma	61/F	-	-	-	-	-	36	Lung

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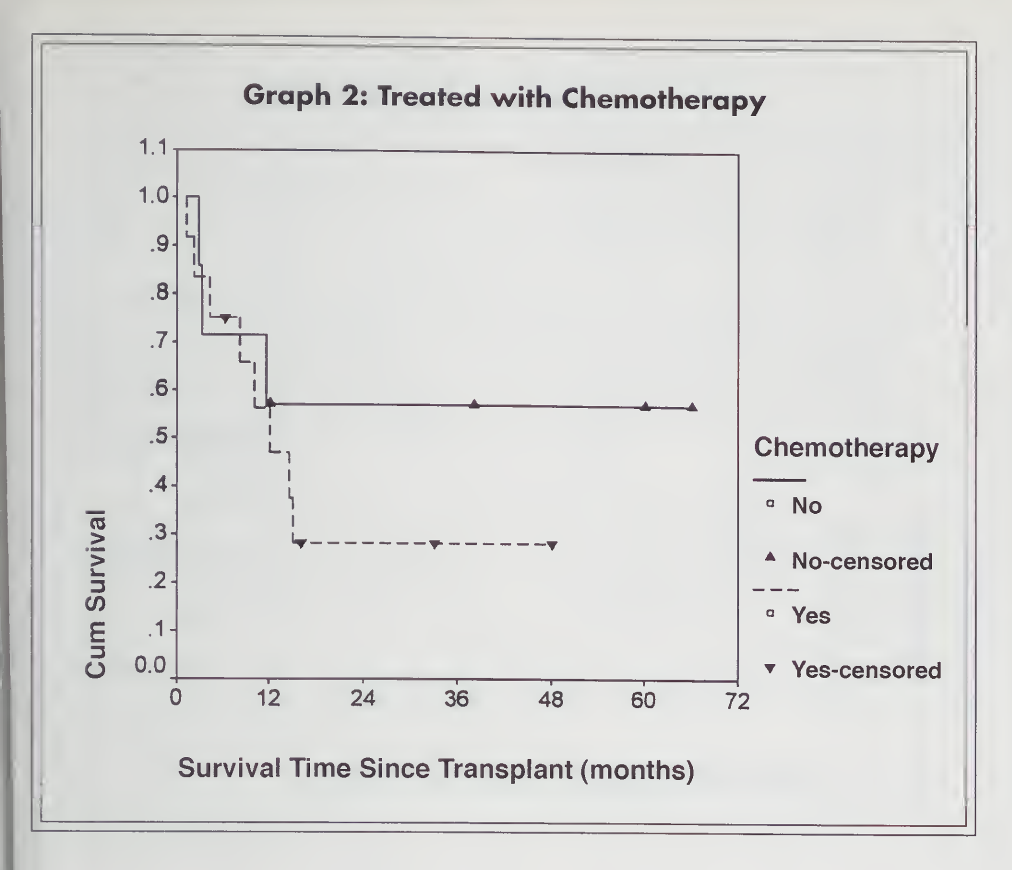
small, the majority of these tumors occur in young adults. These patients are usually otherwise healthy and should be favorable candidates for intensive therapy.

Poole, et al, (7) reviewed the medical literature up to 1983 and reported on 28 patients (mean age of 31.4 years) in whom excision of the primary cardiac malignancy was attempted. Of the 25 patients who were followed, 11 survived for 12 months or longer, with a survival rate of 44% at 12 months. Radiation therapy was given to some patients

Table 3: Patients Treated with Conventional Therapy

Author	Age	Sex	Time from presentotion to diagnosis	Type of tumor	Location of tumor	Resection	Chemo	Radio	Survivol	Mets/ Recurrence	Comments
Perchinsy (31)	-	7M:7F	Meon 16mo Ronge 2- 48mo	Rhobdo-5 Fibro-2 Leiomyo-2 Myxo-2 Synoviol-2 Angio-1	LA-7 RA-6 LV-1	All (Complete in 5)	All	-	All died <1yeor	12 died of mets	
Rodríguez (32)	Meon 47yrs Ronge 33-76yrs	4M:2F	Meon 5mo	Sorcomo-3 Lymphomo-2 Meso-1	RA-1 RV-1, LV-1 Pericord-1 PA-1	1	All	-	Ronge 1-12 mo	-	Lymphomo olive ond well 9yrs post-surgery ond chemo
Molino (33)	Meon 35.7yrs Ronge 4-67yrs	11M:10F	-	Rhobdo-6 Angio-4 Myxo-3 Fibro-2 Spindle cell-3 other-4	RA-19 PA-1 LV-2 AO	9	8	-	Meon 6 mo Ronge 2-9mo	26% hod mets ot time of diognosis	2 Myxosor survived 4.5yrs ond 5.25yrs
Tokoch (34)	Meon 8.1yrs Ronge 3-14yrs	2M:1F	-	Sorcomo-1 Fibro-1 Rhobdo-1	RV RA LA	All (Complete in 2)	2	-	10.3yrs 2.3yrs 6 mo	-	Sorcomo olive 10.3yrs post complete resection, no chemo
Beor & Moodie (35)	Meon 44yrs Ronge 26-63yrs	5M:6F	-	Angio-4 MH-3 Meso-2 Rhobdo-1 Lymphomo-1	RA-5, LA-3 RV-1 LV-1 PA-1 Pericod-1	8 biopsy 3 excision	-	1	Meon 9.7mo	-	1 potient olive well 5yrs post- rodio
Putnom (8)	Ronge 3mo-64yrs	11M:10F	-	Angio-7 MFH-7 Rhobdo-2 Leiomyo-1 Sorcomo-1 Myxosor-1 Fibromyxo-1	LA-12 RA-7 RV-5 LV-2	20 (Complete in 11)	14	None	14% olive ot 24mo Medion 11mo	-	2 lost to follow up; 5olive>24mo 1olive>36mo
Poole (7)	Meon 31.4yrs Ronge 3wks- 70yrs	14M:14F	Meon 4mo Ronge 0.2-18mo	Rhobdo-6 Fibro-5 Myxo-4 Angio-4 Osteo-2 Other-7	LA-11 RA-7 RV-6 PA-1,PV-2 Septum-1	28	8	13	Meon 14mo Ronge 2-55mo	11 mets 6 recurrence	10 died<1yr; 7 olive with o ronge 2-30mo; 11survived >2yrs

KEY
- = No Information
M = Male
F = Female
LA = Left Atrium
RA = Right Atrium
RV = Right Ventricle
LV = Left Ventricle
PA = Pulmonary artery
Ao = Aorta
Pericard = Pericardium
MFH = Malignant fibrohistosarcoma
Rhabdo = Rhabdomyosarcoma
Leiomyo = Leiomyosarcoma
Angio = Angiosarcoma
Myxosar = Myxosarcoma
Chemo = Chemotherapy
Radio = Radiotherapy
mets = metastasis
mo = months



with an apparent benefit and prolongation of life. Chemotherapy, on the other hand, did not affect survival. The causes of death included both metastatic disease and local recurrence with impairment of cardiac function. Putnam et al, (8) reported an actuarial survival of 14% at 24 months for 21 patients with primary sarcomas of the heart who were treated with resection, chemotherapy, or combination of both. In our patient population, (Graph 2) the use of chemotherapy might have been related to a worse outcome. However, this information should be taken cautiously since the patients treated with chemotherapy could have been sicker or have a more aggressive type of tumor.

Development of a malignant neoplasm after any heart transplant is a well-recognized entity (9-12). Post-transplant lymphoproliferative disease (PTLD) is one example of these malignancies with an incidence of 3.4% (13). Whether micrometastases from the initial primary cardiac malignancy might also be encouraged to grow by the immunosuppressive therapy is a matter of conjecture at this point. Nevertheless, current evidence strongly suggests that this is the case (14,15). Crespo et al. (14) described two cases of heart transplantation for cardiac angiosarcomas who died at 8 and 10 months after transplantation with multiple brain metastases. They felt that immunosuppressive treatment encouraged the growth of the metastatic disease with the spread of micrometastases.
Of the cases we collected, 11 patients had metastatic disease, 10 of which subsequently died. Actuarial survival for both groups is shown in Graph 3. The sites of metastases included brain, mediastinum, lung, the donor heart, bone marrow and lymph nodes.
To our knowledge, none of the patients in the heart transplant group developed new malignancies or post-transplant lymphoproliferative disease.

Conclusion

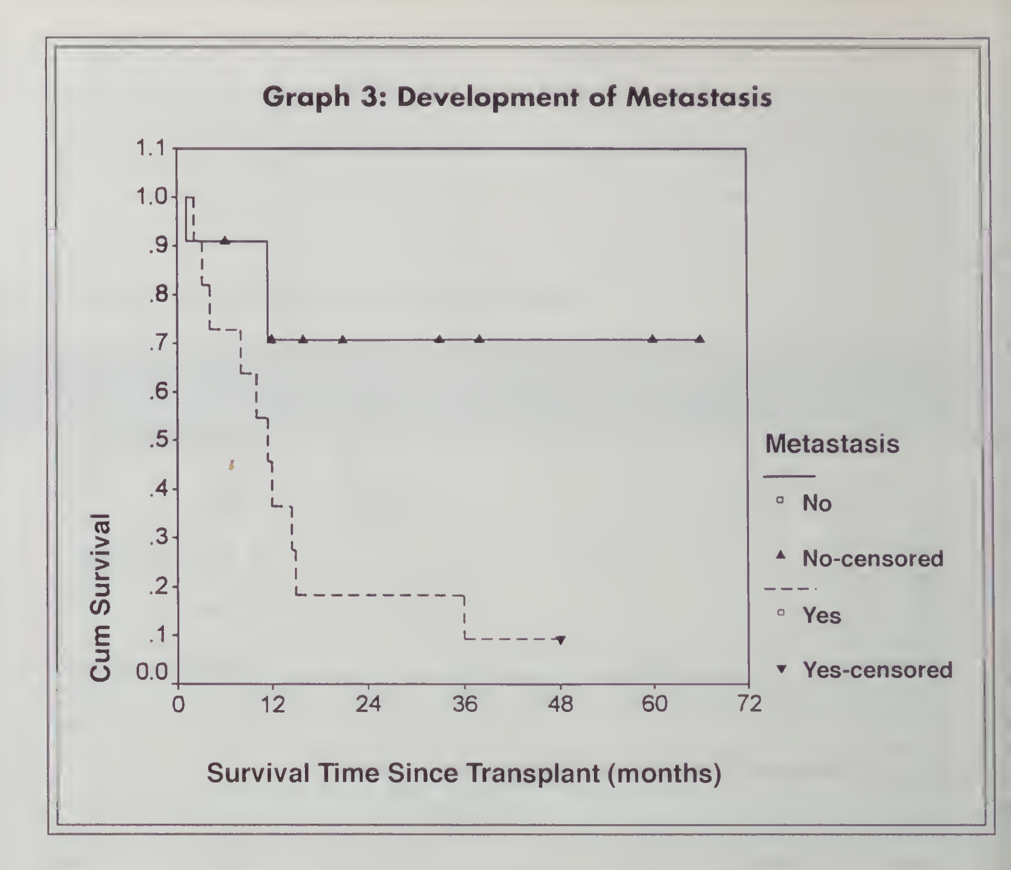
Although known malignancy has previously been a contraindication for heart transplantation, several patients with malignant primary heart tumors have received this treatment modality. Based on the survival rates obtained in this study, when compared to the survival of patients treated with conventional therapy (resection, radiation, chemotherapy, or combination), heart transplantation cannot be ruled out as a treatment for primary cardiac malignant neoplasms based on long term survival of several patients. In spite of the previous considerations, continued concerns of this treatment modality are: (i) the development of new tumors or recurrences in survivors due to the fact that the current immunosuppressive treatment encourages the growth of micrometastases, (ii) the inability of obtaining tumor-free margins at the time of resection or transplantation, (iii) the delay in diagnosis and transplantation, (iv) and the scarcity of donor hearts. In the United States, the average wait for an adult is 6 to 12 months with approximately 25 to 30 % expiring while awaiting for a heart transplant. Early diagnosis and complete resection are important factors toward a better outcome, but they still will not guarantee success since the presence or development of metastasis is a major contributor to death in these patients.
The addition of chemotherapy and radiotherapy to improve survival is equivocal at this time. It will be important to continue to collect data concerning conventional treatment and/or heart transplantation for primary cardiac malignant tumors to determine the best therapeutic approach for these patients.

Abstracto

Los transplantes de corazón se han realizado en varios pacientes con neoplasias malignas primarias del corazón. En este estudio se reúnen y evalúan los casos de este tipo que se han realizado en centros de transplante de los Estados Unidos de América y Canada. Veinticuatro casos se descubrieron. La sobrevivencia general es de 1 a 66 meses después del transplante. La sobrevivencia actual es de 54% a 12 meses, 45% a 24 meses y 35% a 36, 48 y 60 meses, respectivamente. Estos datos indican que el ofrecer un transplante de corazón a un paciente con una neoplasia maligna primaria cardiaca no se puede descartar completamente como alternativa terapéutica.

KEY WORDS
cardiac/ heart transplantation
cardiac/ heart neoplasm
malignant neoplasm/ tumors
orthotopic heart transplant

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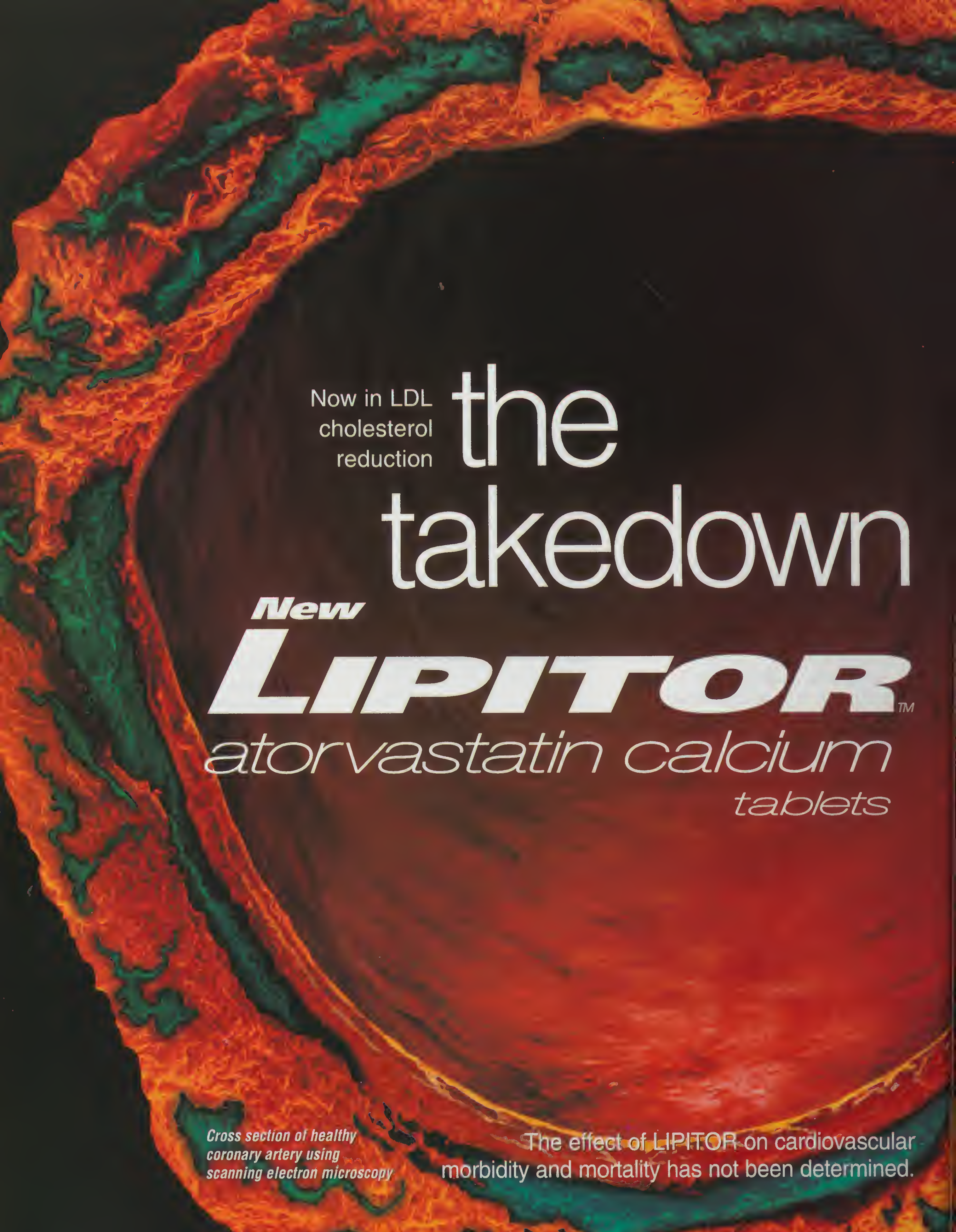
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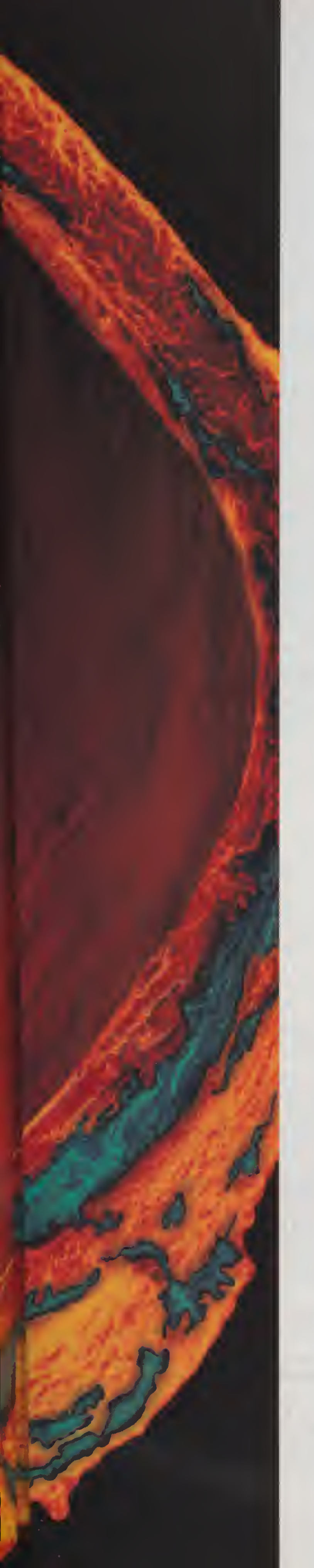
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Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases Hypersensitivity to any component of this medication. **Pregnancy and Lactation**: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes) Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively**. One patient in clinical trials developed jaundice Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin **It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (eg, semiannually) thereafter** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin Patients who develop increased transaminase levels should be monitored until the abnormalities resolve Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS) **Skeletal Muscle — Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class**. Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS) Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS: General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information) **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle). ***Antacid:*** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35% However, LDL-C reduction was not altered. ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected ***Colestipol:*** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone ***Cimetidine:*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20% Patients taking digoxin should be monitored appropriately ***Erythromycin:*** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle) ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20% These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. ***Warfarin:*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. ***Other Concomitant Therapy:*** In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions Interaction studies with specific agents have not been conducted **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females. in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS.** Safety in pregnant women has not been established Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m²). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age. **Geriatric Use**: Treatment experience in adults age ≥70 years with doses of Lipitor up to 80 mg/day has been evaluated in 221 patients The safety and efficacy of Lipitor in this population were similar to those of patients <70 years of age

ADVERSE REACTIONS: Lipitor is generally well-tolerated Adverse reactions have usually been mild and transient In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment:

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment, in <2% of patients treated with atorvastatin in clinical trials.

Body as a Whole: Face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema ***Digestive System:*** Gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** Pneumonia, dyspnea, asthma, epistaxis. ***Nervous System:*** Paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia ***Musculoskeletal System:*** Leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** Urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia ***Metabolic and Nutritional Disorders:*** Hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Caution – Federal law prohibits dispensing without prescription.

Consult package insert before prescribing Lipitor™ (Atorvastatin Calcium) Tablets.

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Artículos de Revisión:

Molecular Biology and Genetics affecting Pediatric Solid Tumors

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Abstract

Since the discovery of oncogenes more than 20 years ago, it has been proven that cancer is a genetically determined disease. Multiple genetic alteration occurs during the course of an illness for neoplasia to develop. Transformation of positive cell growth regulators (oncogenes) and inactivations of negative cell growth regulators (tumor suppressor genes) merge to express a malignant phenotype. These genetic alterations occur as chromosomal translocations, deletions, inversion, amplification or point mutation.

The objective of this review is to introduce basic concepts of molecular biology and describe the molecular genetics and biologic clinical findings of the most important solid malignant tumors in children, namely Neuroblastoma, Wilms and Rhabdomyosarcoma. It is the oncology surgeons responsibility to learn basic molecular genetics and tumor biology to provide rational and appropriate care in the setting of multidisciplinary management. Identifications of new oncogenes will continue to be important milestones in diagnosis, early detection of tumor recurrence, and as potential targets for gene therapy. Fusion proteins generated by mutated translocations are true tumor specific antigens and potential targets for therapy. The predicament is that they are proteins needing therapeutic manipulation within the tumor cell nuclei. Technological advances in molecular and genetics will develop tools necessary to manipulate the cell nuclear DNA and target cancer cell.

Since Watson & Crick (Nobel Laureate, 1962) discovery of DNA double helix structure in 1953 advancements in molecular biology has been revealing.[1] Diagnosis of inherited diseases, cancer staging, markers and therapy have all benefit from technological advancement of this basic science.

Neoplasia continues to be the leading cause of death past the first year of life in children. The most common malignancies in children are leukemias, brain tumors and lymphomas followed by solid tumors. We encounter more than 150 new cases per year of malignancy in children in Puerto Rico, as compared with 7000 new cases in the USA and 200,000 worldwide.[2] Improvement in the prognosis of pediatric solid tumors has been attributed to cooperatives studies creating well-designed tumor treatment protocols, better diagnostic resources along with uniform laboratory methods for measuring tumor markers, cytokines, oncogenes and other biologic factors.

It is believed that cancer is a genetic disease. Multiple genetic alterations must occur during the course of an illness for neoplasia to develop. Transformation of positive cell growth regulators (oncogenes) and inactivation of negative cell growth regulators (tumor suppressor genes) merges to express a malignant phenotype. These genetic alterations occur as chromosomal translocations, deletions, inversion, amplification or point mutation.[3] Oncogenes help in cancer screening, diagnosis, therapy, and follow-up. Cancer can be defined as a progressive series of genetic events that occurs in a single clone of cells because of alteration (mutations) in a limited number of specific genes identified as oncogenes or tumor suppressor genes. Both alleles of a specific gene must be affected during

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cellular division for the alteration to produce a neoplastic cell.

Within this review basic science concepts of molecular biology will be introduced along with description of molecular genetics and biology findings of the most important solid malignant tumors in children, namely Neuroblastoma, Wilms, and Rhabdomyosarcoma. It is the oncology surgeons responsibility to learn basic molecular genetics and tumor biology to provide rational and appropriate care in the setting of multidisciplinary management.

Primer on Molecular Biology and Genetics

The human cell nuclei contain 22 pairs of autosomes and a pair of sex chromosomes. They are numbered according to size, with number 1 being the largest and 22 the smallest. Chromosomes contain a short arm (p) and a long arm (q) divided by the centromere. Chromosomal arms are further subdivided into regions, bands and sub-bands. Chromosomes are tightly bound chains of deoxyribose nucleic acid (DNA). Using cytogenetics techniques arrested cells in metaphase are divided to pair maternal and paternal chromosomes and produce a karyotype mapping.[4]

All living organisms in earth use the same genetic code, mainly DNA and ribose nucleic acid (RNA). DNA contains the genetic information, RNA transport it, and genes are responsible for the production of proteins who maintains cell work and structure. The human genome contains between 50,000 and 80,000 genes with a mean size each of 5,000 base nitrogenous pairs. Only 10% of this gene pool (exons) is available for producing proteins.[5] The rest of the gene pool (known as introns) contains important complex maintenance, repair and control functions. Transcription (t) refers to the process by which the DNA base pair sequence is copied into a messenger RNA (mRNA), also known as the functional unit of a gene. Promoters, enhancers and stop codons are of prime importance during transcription. A series of DNA sequence upstream of the coding sequence act as a promoter to direct the site of transcription initiation, controlling the amount and tissue specificity of mRNA production. Enhancers are responsible for increasing transcription of nearby genes. mRNA translates the information into a sequence of amino acids that will ultimate form a protein. Stop codons are triple nucleotide base coding sequences that end translation.[6] The final product of translation is a protein that is the building structure of cell stability and function.

Besides the nucleus, DNA is also found in the mitochondria, maternally inherited and containing two ribosomal RNA genes, 22 transfer RNA genes and 13 genes for proteins involved in oxidative phosphorylation. The pathway of mitochondrial fatty acid oxidation contributes to energy homeostasis, especially in the heart, the liver and skeletal muscle. Defect from phosphorylation by a maternal inherited disease is known as a mitochondrial fatty acid oxidation disorder, transmitted as an autosomal recessive trait lead to myopathies (cardiac and skeletal), liver dysfunction and encephalopathies.[6, 7]

DNA, RNA, nucleic acids and proteins can be separated from each other using electrophoresis. DNA strands are separated by heating and rejoined by cooling. Sequence of nucleic acids is then detected by a technique known as hybridization since single stranded nucleic acids molecules will form a double-stranded molecule when they encounter a complementary strand. Using cloning, an unlimited quantity of DNA can be made. For example, Insulin, Somatostatin, Tumor Necrosis Factor, Lymphokines and Growth Factor are produced by vector induced cloning.[5]

Heat causes the separation of the hydrogen bonds that holds the two strands of DNA. With cooling of temperature the hydrogen bonds forms between new nucleotides bases added in the solution, called primers, and the bases on each strand. Using DNA polymerases, two identical double stranded molecules of DNA are made. A machine repeats this heating/ cooling process several times creating millions of identical molecules. This is known as polymerase chain reaction (PCR). Amplifying DNA fragments by PCR in a thermocycler is a common application of surgical research. Chemistry Nobel prize winner Kary Mullis discovered PCR in 1985 making possible the study of ancient DNA.[8] With PCR an exponential number of specific DNA sequences can be produced without resorting to cloning, but the sequence of DNA of interest to copy must be known beforehand. Also it can identify whether a given sequence of DNA exists in a clinical specimen. PCR has been of enormous help in the prenatal diagnosis of Cystic Fibrosis, ß-Thalassemia, and Hemophilia. PCR has also helped in identifying chromosomal abnormalities, detecting mutations in oncogenes, tumor suppressor genes and identifying the presence of RNA or DNA tumor viruses.[6,9]

Cells differ from each other depending on the quality and quantity of mRNA they produce. This mRNA has two types of expression:

1- Housekeeping genes - mRNA encoding for common proteins required for basic structure (i.e., actin, ribosomal protein) and metabolic function (i.e., glycolytic enzymes).

2- Tissue specific mRNA encoding for morphological characteristics (skeletal muscle, heart muscle, etc.) and specific function (insulin production) of cells.[10]

A genetic lesion in the DNA of a cell may alter the expression of one or more mRNA encoding for a protein that regulates cell behavior altering the morphology and function of the cell. Altered cells are susceptible to further mutations leading to malignant solid tumors and leukemias. Oncogenes are genes produced when this DNA lesion and the subsequent mRNA change of expression occur.
This oncogenes code for a protein. Cell growth can be affected by the action of these proteins products acting as growth factors, membrane-bound protein kinases, membrane-bound signal transducers and nuclear transcription factors.
The largest family of oncogenes actually known are those that encode transcription factors, proteins that bind to regulatory sequences of target genes and stimulate (increasing gene expression) or inhibit transcription.[2] Other important families include genes that encode protein kinases, proteins involved in programmed cell death (apoptosis), and proteins with tumor suppressor functions whose loss can contribute to tumorigenesis.

Major genetic changes that promote tumorigenesis have been classified according to their mechanism of action into:

1- Proto-oncogene becomes oncogenic when it is translocated to a transcriptional active site that promotes dysregulated expression. An example occurs in most cases (80%) of Burkitt lymphoma t(8;14) when myc is translocated to the Ig heavy chain gene locus causing myc over expression and resulting in abnormal interactions with other cellular proteins.[2]

2- Gene fusion leading to the generation of chimeric transcription factors creating potent trans-activators inducing tumors. Examples are alveolar rhabdomyosarcoma t(2;13)(q35q14) and t(1;13)(p36q14) causing a worse prognostic tumor.

3- Fusion proteins with altered tyrosine kinase activity are another example how translocation lead to cancer. For example t(9;22), the Philadelphia chromosome, occurs in 95% of chronic myelogenous leukemia cases.

4- Inactivation of tumor suppressor genes causes loss of function of these proteins, which normally act to supress cell growth, contributing to transformation by removing key restraints on cell proliferation. One example is the retinoblastoma (Rb) protein.

5- Other rare mechanisms of childhood cancer development are gene amplification, defects in DNA repair, and point mutations in signals transduction genes.

While studying retinoblastoma, an autosomal dominant inherited disease, it was found that a chromosomal defect in the tumor cells led to loss or inactivation of a gene involved in cell growth regulation. Deregulation of this tumor-suppressor gene (also known as recessive oncogene or anti-oncogene) resulted in cell growth and proliferation predisposing the individual to neoplasia.[11] Oncogenes and tumor-suppressor genes can dictate the prognosis and alter therapy. To identify a tumor-suppressor gene you need to study: 1) families predisposed to the specific tumor, 2) nonrandom chromosomal aberration of the tumor, 3) loss of heterozygosity, and 4) ability to supress a tumor phenotype in cell culture by fusion with normal cells.[11]

Using Northern Blot you can isolate mRNA or if unstable it can be copied enzymatically into a stable molecule of complementary DNA (cDNA). Using cDNA subtraction hybridization or subtraction cloning you can isolate tissue specific and tumor specific genes such as: embryonic development genes, cell-cycle genes (progression, differentiation, senescence and apoptosis), cancer specific genes (oncogenes), and specific chromosomal genes involved in a disease.[10]

Gene therapy, or correction of a human disease by introducing genetic material into an organism is the ultimate goal in curing inherited diseases of mankind. This can occur at somatic or germline level. By germline we refer to all cells in the body, though is actually not currently feasible.[6, 12] At the somatic level a nucleic acid is delivered to a host cell using a vector, usually a retrovirus that involve reverse transcription of its carrying RNA curing genome into DNA and affects the change.

The main cytogenetic changes associated with development of malignancy are: deletions, translocations and inversions.[13] Deletions (d) often result in loss of a tumor suppressor gene. Translocation (t) and inversions (I) occur commonly in tumor cells. Genetic material from one chromosome is exchanged into

another chromosome. Translocations can lead to:

1- Over expression of an oncogene when the gene for a T-cell receptor or an immunoglobulin protein comes to lie near a proto-oncogene or,

2- the breaks occurs within a gene on each chromosome involved creating a fusion oncogene encoding a chimeric protein. Over expression of a gene can also occur by gene amplification: small pieces of DNA chromosomes that lack a centromere and segregate randomly at cell division or long segments within chromosomes that stain in a uniform pattern. Other tumor related aberrations are deletions, inversion and insertions.

Tumor cells can gain or lose DNA material. Flow cytometry can determine the DNA index (DI) by comparing the total DNA in a tumor cell with a normal cell. A normal cell with 46 pairs of chromosomes is diploid and contains a DI of one. Tumors can be hyperdiploid (DI > 1) or hypodiploid (DI < 1).

The actors

Improvements in the outcome of pediatric solid tumors have been the results of:

1- Multidisciplinary cooperative studies from such groups as the Pediatric Oncology Group (POG), Children Cancer Study Group (CCSG), National Wilms Tumor Study Group (NWTSG), Intergroup Rhabdomyosarcoma Study (IRS), and the recently merged single national pediatric organization, the Children's Oncology Group (COG).

2- Physicians dedicated to cancer care that are willing to get together and discuss cases in planning tumor conferences regularly.

3- Better diagnostic resources (imaging and pathology).

4- Feasibility of measuring tumor markers, cytokines, oncogenes and important biologic and genetic tumor factors.[14]

The most common malignant solid tumors in children comprised Wilms tumor, Neuroblastoma and Rhabdomyosarcoma. Each malignancy will be addressed in what pertains characteristic molecular biologic principles affecting diagnosis and therapy.

Wilms Tumor (WT)

Wilms tumor (WT) is the most common intra-abdominal malignant tumor in children affecting more than 400 children annually in the USA. It has a peak incidence at 3.5 years of age. WT present as a large abdominal or flank mass with abdominal pain, asymptomatic hematuria, and occasionally fever. Other presentations include malaise, weight loss, anemia, left varicocele (obstructed left renal vein), and hypertension. Initial evaluation consists of: Abdominal films, Ultrasound, IVP, urinalysis, Chest-X-rays and Computed Tomography. The presence of a solid, intrarenal mass causing intrinsic distortion of the calyceal collecting system is virtually diagnostic of Wilms tumor. Doppler sonography of the renal vein and inferior vena cava can exclude venous tumor involvement. Metastasis occurs most commonly to lungs and occasionally to liver. Operation is both for treatment and staging to determine further therapy. Following NWTSG's recommendation primary nephrectomy is done for all but the largest unilateral tumors and further adjuvant therapy is based on the surgical and pathological findings.[15] Important surgical caveats consist of using a generous transverse incision, performing a radical nephrectomy, exploring the contralateral kidney, avoiding tumor spillage, and sampling suspicious lymph nodes. Nodes are biopsied to determine extent of disease. WT staging by NWTSG consists of:

Stage I- tumor limited to kidney and completely resected.
Stage II- tumor extends beyond the kidney but is completely excised.
Stage III- residual non-hematogenous tumor confined to the abdomen.
Stage IV- hematogenous metastasis.
Stage V- bilateral tumors.

Further treatment with chemotherapy or radiotherapy depends on staging and histology (favorable vs. non-favorable) of the tumor. Non-favorable histologic characteristics are: anaplasia (three times enlarged nucleus, hyperchromatism, mitosis), sarcomatous or rhabdoid degeneration. The success in managing WT has been remarkable the result of stratification, registry and study from the NWTSG. Disease-free survival is 95% for Stage I and approximately 80% for all patients. Prognosis is poor for those children with lymph nodes, lung and liver metastasis.[16]

WT occurs either sporadic (95%), familial (1-2%) or associated with a syndrome (2%). Such syndromes predisposing to WT are WAGR (Wilms, aniridia, genitourinary malformation and mental retardation), Beckwith-Wiedemann Syndrome (gigantism, macroglossia, pancreas cell hyperplasia, BWS),

and Denys-Drash Syndrome (male pseudohermaphrodite, nephropathy and Wilms tumor, DDS). They tend to occur in younger patients. Sporadic WT is associated in 10% of cases with isolated hemihypertrophy or genitourinary malformations such as hypospadia, cryptorchidism and renal fusion.[17] Bilateral synchronous kidney tumors are seen in 5-10% of cases. Routine abdominal ultrasound screening every six months up to the age of eight years is recommended for children at high risk for developing WT such as the above-mentioned syndromes.

It was originally thought that WT developed after the two-hit mutational model developed for retinoblastoma: When the first mutation occurs before the union the sperm and egg (constitutional or germline mutation) the tumor is heritable and individuals are at risk for multiple tumors. Nonhereditary WT develops as the result of two-postzygotic mutations (somatic) in a single cell. The two-event hypothesis predicts that susceptible individuals such as familial cases, those with multifocal disease and those with a congenital anomaly have a lower median age at diagnosis than sporadic cases. It is now believed that several genes mutations are involved in the overall WT pathogenesis.[15, 18]

Loss of whole portions of a chromosome is called loss of heterozygosity (LOH), a mechanism believed to inactivate a tumor-suppressor gene. WT has been found 50% of the time to contain LOH at two genetic loci: 11p13 and 11p15. WT will develop in 30% of WAGR children. Children with the WAGR association shows a deletion in the short arm of chromosome 11 band 13 (11p13) but a normal 11p15 region. Up to a third of sporadic WT have changes in the distal part of chromosome 11, a region that includes band p13. The region of the deletion has been named the WT1 gene, a tumor suppressor gene that also forms a complex with another known tumor-suppressor, p53. WT1 gene express a regulated transcription factor of the zinc-finger family proteins restricted to the genitourinary system, spleen, dorsal mesentery of the intestines, muscles, central nervous system (CNS) and mesothelium.[18] WT1 is deleted in all WAGR syndromes cases. The important association of WT1 mutation and WAGR syndrome with intralobar nephrogenic rests immediately suggest that WT1 expression be necessary for the normal differentiation of nephroblasts.[19] Only five to 10% of sporadic WT have thus far been shown to harbor WT1 mutations. Inactivation of WT1 only affects organs that express this gene such as the kidney and specific cells of the gonads (Sertoli cells of the testis and granulosa cells of the ovary).[15] WT1 has been shown to cause the Denys-Drash syndrome. Most of the mutations described in DDS patients are dominant missense mutations.

A small subset of BWS has a 11p15 duplication or deletion. The region 11p15 has been designated WT2 gene and is telomeric of WT1. Beckwith-Wiedemann form of WT is also associated with IGF2, an embryonal growth-inducing gene. This might prove that two independent loci may be involved in tumor formation. Candidates genes include insulin-like growth factor II gene (IGFII) and the tumor suppressor gene H19.[15] A substantial fraction of WT (without LOH at the DNA level) has been found to have altered imprints with resultants over expression of IGFII and loss of expression of the tumor suppressor H19. IGFII may be operating like an oncogene by perpetuating nephroblast and may account for the perilobar rests observed in BWS patients.[19]

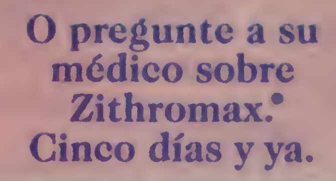
A gene for a familial form (FWT1) of the tumor has also been identified in chromosome 17q.[20] There also might be a gene predisposing to Wilms tumor at chromosome 7p, where constitutional translocations have been described. Mutation in p53 is associated with tumor progression, anaplasia and poor prognosis. Most WT are probably caused by somatic mutations in one or more of the increasing number of WT genes identified.[17]

A few chromosomal regions have seen identified for its role in tumor progression. LOH at chromosome 16q and chromosome 1p has been implicated in progression to a more malignant or aggressive type Wilms tumor with adverse outcome. This occurs in approxi-mately 20% of patients with WT. These children have a relapse rate three times higher and a mortality rate twelve times higher than WT without LOH at chromosome 1p. p53 is also associated with the so called anaplastic unfavorable histology.

Patients with WT and a diploid DNA content (indicating low proliferation) have been found to have an excellent prognosis. Hyperdiploidy (high mitotic activity) is a poor prognostic feature of Wilms tumor, rhabdomyosarcoma and Osteosarcoma.

Nephrogenic rests are precursor lesions of WT. Two types are recognized: perilobar nephrogenic rests (PLNR) limited to the lobar periphery, and intralobar nephrogenic rests (ILNR) within the lobe, renal sinus or wall of the pelvocaliceal system. The strong association between ILNR, aniridia and Denys-Drash syndrome where

"Su niño tiene otra infección bacteriana de oídos. Puede que necesite un antibiótico...y recuerde, tiene que tomárselo todo".





Si el médico le receta un antibiótico para la infección bacteriana de oídos de su niño (otitis media aguda), pregúntele si Zithromax es adecuado para él/ella.

El UNICO ANTIBIOTICO PARA TOMAR UNA VEZ AL DIA POR CINCO DIAS.

A diferencia de otros antibióticos, Zithromax se administra solamente una vez al día por cinco días. Y cinco días son tan efectivos como la terapia convencional de diez días porque el efecto de Zithromax continúa por varios días después de la última dosis.

Zithromax tiene un agradable sabor a cereza que a los niños les gusta y se tolera bien. Los efectos secundarios más comunes son diarrea (2%), dolor abdominal (2%), vómitos (1%) y náusea (1%). Aunque las reacciones alérgicas son poco frecuentes, de ocurrir, descontinúe el uso de este medicamento y consulte con su profesional de la salud. Para detalles completos, véase un breve resumen en la próxima página.

PREGUNTE A SU MEDICO SI ZITHROMAX ES ADECUADO PARA SU NIÑO.

Para mayor información sobre Zithromax y un folleto gratis sobre el desarrollo del lenguaje y la audición,

llame al 1-800-587-DAYS.
O visítenos en www.KidsEars.com





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Augmentin (amoxicillin/clavulanate potassium) is a registered trademark of SmithKline Beecham Pharmaceuticals

Zithromax®

(azithromycin for oral suspension)

ONCE DAILY FOR 5 DAYS

ZITHROMAX®
(azithromycin for oral suspension)

BRIEF SUMMARY

INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see **WARNINGS**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.* (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION.**)

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION.**)

NOTE: **Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).**

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy. (For specific dosage recommendations, see **DOSAGE AND ADMINISTRATION.**)

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX® may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

ZITHROMAX® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See **CONTRAINDICATIONS.**) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function.

There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes,* in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for Patients: Patients should be cautioned to take ZITHROMAX® suspension at least one hour prior to a meal or at least two hours after a meal. This medication should not be taken with food.

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Drug Interactions: Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Azithromycin did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised.

Digoxin—elevated digoxin levels.

Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolam—decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

Drugs metabolized by the cytochrome P^{450} system—elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day). These doses, based on a mg/m² basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use: (**INDICATIONS AND USAGE.**)

Acute Otitis Media (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults.

Pharyngitis/Tonsillitis (dosage regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted.

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients (adults and children) from the multiple-dose clinical trials discontinued ZITHROMAX® (azithromycin) therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely.

Clinical: Adults: *Multiple-dose regimen:* Overall, the most common side effects in adult patients receiving a multiple-dose regimen of ZITHROMAX® were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other side effects occurred in patients on the multiple-dose regimen of ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.
Genitourinary: Monilia, vaginitis, and nephritis.
Nervous System: Dizziness, headache, vertigo, and somnolence.
General: Fatigue.
Allergic: Rash, photosensitivity, and angioedema.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX® were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX® with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX® were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Children: *Multiple-dose regimens:* The types of side effects in children were comparable to those seen in adults, with different incidence rates for the two dosage regimens recommended in children.

Acute Otitis Media: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%).

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (5.8%), abdominal pain, vomiting, and nausea (1.9% each), and rash (1.6%).

Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%), and headache (1%).

With either treatment regimen, no other side effects occurred in children treated with ZITHROMAX® with a frequency of greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, flatulence, and gastritis.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, insomnia.
General: Fever, fatigue, malaise.
Allergic: Rash.
Skin and Appendages: Pruritus, urticaria.
Special Senses: Conjunctivitis.

Post-Marketing Experience: Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria.
Cardiovascular: Arrhythmias including ventricular tachycardia.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration.
General: Asthenia, paresthesia.
Genitourinary: Interstitial nephritis and acute renal failure.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice.
Nervous System: Convulsions.
Skin/Appendages: Rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis.
Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste disturbances.

Laboratory Abnormalities: Adults: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT); with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

Children: Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Acute Otitis Media and Community-Acquired Pneumonia: The recommended dose of ZITHROMAX® for oral suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day).

Pharyngitis/Tonsillitis: The recommended dose for children with pharyngitis/tonsillitis is 12 mg/kg once a day for 5 days (not to exceed 500 mg/day).

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.
ZITHROMAX® for oral suspension should not be taken with food.

More detailed professional information available on request.
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the WT1 zinc finger gene has been implicated suggests that this locus might be linked to the pathogenesis of ILNR. Also the association between BWS and some cases of hemihypertrophy with abnormalities of more distant loci on chromosome 11p raises the possibility that the putative WT2 gene might be more closely linked to PLNR.[21]

An advantage of genetic testing is that children with sporadic aniridia, hemihypertrophy or the above discussed syndromes known to be at high risk for developing WT can undergo screening of the germline DNA. This might identify if they harbor the mutation and need closer surveillance for tumor development.

Neuroblastoma (NB)

Neuroblastoma (NB) is the most common extracranial solid tumor in infants. More than 500 new cases are diagnosed annually in the United States. Most neuroblastomas (75%) arise in the retroperitoneum (adrenal gland and paraspinal ganglia), 20% in the posterior mediastinum, and 5% in the neck or pelvis. NB is a solid, highly vascular tumor with a friable pseudocapsule. Most children present with an abdominal mass, and one-fourth have hypertension. Other have: Horner's syndrome, Panda's eyes, anemia, dancing eyes or vaso-intestinal syndrome. Diagnosis is confirmed with the use of simple X-rays (stipple calcifications), Ultrasound, and CT-Scan. Work-up should include: bone marrow, bone scan, myelogram (if there is evidence of intraspinal extension), and plasma/urine tumor markers level: vanillylmandelic acid (VMA), homovanillic acid (HVA) and dopamine (DOPA).

Management of NB depends on the stage of disease at diagnosis. Localized tumors are best managed with surgical therapy. Partially resected or unresectable cases need chemotherapy a/o radiotherapy after establishing a histologic diagnosis. Independent variables determining prognosis are age at diagnosis and stage of disease. The Evans classification for NB staging comprised:

Stage I - tumor confined to an organ of origin.
Stage II - tumor extending beyond an organ of origin, but not crossing the midline. Ipsilateral lymph nodes may be involved.
Stage III - tumor extending beyond midline. Bilateral lymph nodes may be involved.
Stage IV - remote disease involving skeleton, bone marrow, soft tissue or distant lymph nodes.
Stage IVS - same as stage I or II with presence of disease in liver, skin or bone marrow.

Young children with stage I/II have a better outcome. A poor outcome is characteristic of higher stages, older patients and those with bone cortex metastasis. Other prognostic variables are: the site of primary tumor development, maturity of tumor, presence of positive lymph nodes, high levels of ferritin, neuron-specific enolase, and diploid DNA.[22-29]

Neuroblastoma is a malignant tumor of the postganglionic sympathetic system that develops from the neural crest: sympathetic ganglion cells and adrenal gland. In vitro three cell types have been identified:

1- neuroblastic (N-type) cells that are tumorigenic. These cells are responsible for producing cathecolamines and vasoactive substances which help in diagnosis and follow-up therapy.

2- the Schwannian or substrate-adherent (S-type) cells that are non-tumorigenic, and the

3- intermediate I-cells.[30]

NB can behave seemingly benignly and undergo spontaneous regression, mature into a benign ganglioneuroma or most commonly progress to kill its host. This disparate behavior is a manifestation that we are dealing with related tumors with differently genetic and biological features associated with a spectrum of clinical behaviors.[31]

Conclusive associations with environmental factors have not been proved in NB. Hereditary factors are important in NB since a few cases exhibit predisposition following a dominant pattern of inheritance. The most characteristic cytogenetic abnormality of neuroblastoma is deletion of the short arm of chromosome 1 in locus 36 (1p36) occurring in 50 to 70% of primary diploid tumors. LOH of the short arm of chromosome 1 is also associated with an unfavorable outcome, suggesting that a tumor suppression gene may be found in this region.[2,31] The common region of deletion or LOH resides at the distal end of the short arm of chromosome 1 from 1p36.2 to 1p36.3. Loss or inactivation of a gene at this site is critical for progression of neuroblastoma.[31] A few candidate genes from this site have been mapped. LOH in chromosome 14 long arm (14q) has also been identified in 25-50% or neuroblastoma cells studied but no clinical behavior has been identified with this finding. Gain of chromosome 17 is associated with more aggressive tumors.

Another consistent chromosomal aberration identified in 25 to 30% of NB cells is the presence of double-minute chromosomes, small fragments of chromatin containing multiple copies of the oncogene N-myc produced by amplification. N-myc protooncogene is found on chromosome 2p and its activation results in tumor formation.
The amplified N-myc sequence is found on extrachromosomal double minutes (DM) or on homogeneous staining regions (HSR) involving different chromosomes in neuroblastoma (N-type) cell lines. N-myc amplification is strongly associated with advance stages of disease, rapid tumor progression and poor outcome independent of the stage of the tumor or the age of the patient. NB tumors associated with N-myc amplification needs aggressive therapy. N-myc amplification associated with deletion of 1p is correlated with a poor outcome. Deletion of the long arm of chromosome 1 (1q-) is also a poor prognostic sign.[11]

Though most NB cells are diploid, a good number of them are hyper-diploid or triploid. Hyperdiploidy is a good prognostic feature of NB and embryonal rhabdomyosarcoma in infants, while diploid tumors at any age and hyperdiploid in older patients carry a worse prognosis requiring more intensive treatment.[31]

Neuroblast cells needs nerve growth factor (NGF) for proper differentiation. NB tumor cells do not respond to NGF or do not express the receptor. This receptor consists of three transmembrane tyrosine kinase receptors (TRK-A, TRK-B, and TRK-C), known together as the TRK receptor. TRK-A is detected in 90% of NB cells and correlates inversely with N-myc expression. High TRK-A levels correlate strongly with improved survival and plays a role in the propensity for tumors to regress or differentiate into a more benign nature. TRK-B is associated with more matured tumors and TRK-C with lower stage tumors. Alteration in the NGF receptor function or expression promotes tumorigenesis. In conclusion, high levels of TRK expression are associated with better prognosis, earlier stage, lower patient age and lack of N-myc expression.[31]

Neuroblastomas in newborns, cystic tumors, bilateral tumors in infants, and infants less than one year of age with neuroblastoma stage IV-S can undergo neuronal cell differentiation with spontaneous regression. It is thought that high level of TRK-A found in this cases might explain differentiation and regression as high level of this glycoprotein is associated with a favorable prognosis. Regression might be associated with non-affected tumor cell apoptosis.

Other biological markers associated with NB are the multidrug resistance-related protein (MRP) gene, telomerase activity and bcl-2 gene activity. MRP shows a strong correlation with an advanced clinical stages and poor prognosis. High telomerase activity is associated with poor prognosis and high N-myc amplification.[31]
The bcl-2 gene produces a protein that prevents neuronal cell death (apoptosis) and promotes tumor progression. Bcl-2 expression is associated with a poor outcome. Apoptosis in NB may result in tumor progression.

Taking into consideration the above cytogenetics changes of NB cells we can assign patients to three genetically distinct risk groups as suggested in Table 1.[31] Genetic markers provide a means of classifying tumors that may be histologically similar. Genetic analysis may permit to redirect therapy according to prognosis in NB.

The RET proto-oncogene is a protein tyrosine kinase gene (Ret protein) expressed in the cells derived from the neural crest.
The activation of RET involves a chromosomal inversion of the long arm of chromosome 10 that juxtaposes the tyrosine kinase encoding domain of RET to the amino terminal sequences of at least three unrelated genes. Germline mutations in the RET gene have been associated with neuroblastoma, pheochromocytoma, multiple endocrine neoplasia (MEN) 2, familial medullary thyroid carcinoma (MTC), radiation-induced thyroid papillary carcinoma, and recently Hirschsprung's disease. RET analysis is a suitable method to detect asymptomatic children with MEN at risk to develop MTC allowing us to consider thyroidectomy at a very early stage of neoplasm development (C-cell hyperplasia) or prophylactically.[32-37]

High levels of neuron specific enolase and serum ferritin levels are associated with a poor prognosis in NB. Nm-23 and ganglioside GD2 are still other tumor markers associated with poor outcome, active disease and tumor progression.[14]

Rhabdomyosarcoma (RMS)

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in infants and children, represents about 5-15% of all malignant solid lesions. It has a peak incidence before the age of five years, and a second surge during early adolescence. Head, neck and pelvic malignancies are more prevalent in infancy and early childhood, while trunk, extremity and paratesticular sites are largely a disease of adolescents. RMS arises from a primitive cell type and occurs in mesenchymal tissue at almost any body site excluding brain and bone.

Table 1. Neuroblastoma Genetically Distinct Risk Groups Categories.[31]

	Group 1	Group 2	Group 3
N-myc	no amplification	no amplification	amplified
DNA ploidy	hyperdiploid	diploid	diploid
1p LOH	< 5%	25-50%	80-90%
14q LOH	< 5%	25-50%	< 5%
TRK	high TRK-A & TRK-C; low TRK-B	Low	low TRK-A & TRK-C; high TRK-B
Age	< 1 year	> 1 year	1-5 years
Stage	I, II IVS	III, IV	III, IV
3-year survival	95%	25-50%	< 5%

The predominant histologic type in infants and small children is embryonal rhabdomyosarcoma, occurring in the head and neck, genitourinary tract and retroperitoneum. Embryonal RMS is associated with a favorable prognosis. Botryoid RMS is a subtype of the embryonal variety, which ordinarily extends into body cavities such as bladder, nasopharynx, vagina, or bile duct. The alveolar cell type, named for a superficial similarity to the pulmonary alveoli, is the most common form found on the muscle masses of the trunk and extremities, and is seen more frequently in older children and young adults. Alveolar RMS is associated with a poor prognosis. This unfavorable prognosis is the result of early and wide dissemination, bones marrow involvement and poor response to chemotherapy.

Clinical findings, diagnostic evaluation and therapy depend upon location of the primary tumor and are beyond the scope of this review. Head and neck RMS are most common and occur in the orbit, nasopharynx, paranasal sinuses, cheek, neck, middle ear, and larynx. Most are treated by simple biopsy followed by combined therapy or preoperative chemotherapy and radiation followed by conservative resection. Operations for extremity lesions include wide local excision to remove as much of gross tumor as possible. The trend in management is more chemotherapy with conservative surgical therapy. Survival has depended on primary site, stage of disease, and treatment given.[38-40]

Most RMS occurs sporadically. Approximately 5% are associated to syndromes such as Beckwith-Wiedemann with LOH at the 11p15 locus, Li-Fraumeni, the neurofibromatosis-NF1 gene located on 17q11, Basal Cell Nevus, and the Fetal Alcohol syndrome. Other risk factors in the development of RMS include maternal use of marijuana and cocaine, exposure to radiation, and maternal history of stillbirth.[14]

Alveolar and embryonal RMS are the most genetically studied sarcomas in children. The expression of a number of human paired box-containing (PAX) genes has been correlated with various types of RMS. In alveolar RMS novel fusion genes encoding chimeric fusion proteins have been identified.
The most consistent genetic mutation identified in more than 70% of alveolar RMS is translocation of chromosomes 2 and 13, t(2;13)q35-37;q14). The PAX3 loci in chromosome 2 fuses to the FKHR (fork head in rhabdomyosarcoma) domain of chromosome 13 creating a powerful chimeric PAX3-FKHR gene that encodes an 836 amino acid fusion protein. This information is obtained using reverse transcriptase PCR assays of alveolar RMS or by protein immunoprecipitation with PAX3 and FKHR antisera. The PAX3-FKHR protein is an active transcription factor.
The t(2;13) activates the oncogenic potential of PAX3 by dysregulating or exaggerating its normal function in the myogenic lineage and affecting the cellular activities of growth, differentiation and apoptosis. Another of the reported translocation is t(1;13)(p36;q14) involving chromosome 1 and 13 in 10% of alveolar RMS.[13, 41-43]
In this variant, Chromosome 1 locus encoding PAX7 fused to FKHR in chromosome 13 resulting in another chimeric transcript PAX7-FKHR. PAX7-FKHR tumors tend to occur in younger patients, are more often in the extremity, are more often localized lesions and are associated with significantly longer event-free survival. Still, a small subset of alveolar RMS does not contain either fusion mutation. The PAX3-FKHR and the variant PAX7-FKHR fusions are associated with distinct clinical phenotypes. Identification of fusion gene status by PCR is a useful diagnostic tool in differentiating RMS from other round cell tumors.[44]

Embryonal RMS contains frequent allelic loss on chromosome 11 (11p15), a genetic feature specific for this type of tumor. Allelic loss is manifested by the absence of one of

the two signals in the tumor cells indicating a genetic event such as a chromosome loss, deletion, or mitotic recombination that eliminates one allele and the surrounding chromosomal region. The smallest affected region has been localized to chromosomal region 11p15.5.[43] The presence of a consistent region of allelic loss is often indicative of the presence of a tumor suppressor gene inactivated in the associated malignancy. The mechanism for inactivation of tumor suppressor genes is postulated to be a two-hit scenario in which both copies of the gene are sequentially inactivated: a small point mutation inactivates one of the two alleles, preferably the maternal side allele, and the allelic loss event inactivate the second allele (the paternal allele). This leads to over expression of the insulin-like growth factor II gene known to play a role in the development of embryonal tumors.

Other alterations associated with embryonal RMS are distinct patterns of chromosomal gains (chromosomes 2,7,8,12,13,17,18, and 19) in contrast with alveolar RMS which shows genomic amplification of chromosomal region 12q13-15 in 50% of cases. Notably, these distinct changes predominantly involved chromosomes 2, 12, and 13 in both subtypes.[45] Additionally embryonal RMS cases shows mutations of members of the RAS gene family, a second proto-oncogene. Both tumors share alterations in the p53 gene at the germline level contributing to increase susceptibility to other tumors characteristics of the Li-Fraumeni syndrome. There is also greater over expression of c-myc in alveolar RMS when compared with embryonal RMS.[46] All this favors a multi-step origin of RMS tumors generating phenotypic changes of growth autonomy, abnormal differentiation and motility.[43, 45]

The Li-Fraumeni familial cancer syndrome is manifested by increased susceptibility of affected relatives to develop a diverse set of malignancies during early childhood.
The major features of the syndrome include breast cancer, osteosarcoma, rhabdomyosarcomas of soft tissue, glioblastoma, leukemia and adrenal cortical carcinoma.
More than one-half of the cancers overall and nearly one-third of the breast cancers were diagnosed before 30 years of age.
Among females, breast cancer is the most common. Germline mutations within a defined region of the p53 gene have been found in families with the Li-Fraumeni syndrome. Persistence of the mutation in the germline suggests a defect in DNA repair in the family member first affected. Asymptomatic carriers of p53 germline mutation needs closed evaluation and follow-up for early detection and treatment in case neoplasia develops.[47-51]

Conclusions

Cancer is a genetically determine disease. Genes are involved in cancer induction and progression. A change in the cell DNA by way of translocation, deletion or inversion give rise and maintains disease progression. Identifications of new oncogenes will continue to be important milestones in diagnosis, early detection of tumor recurrence, and as potential targets for gene therapy. Fusion proteins generated by mutated translocations are true tumor specific antigens and potential targets for therapy.
The predicament is that they are proteins needing therapeutic manipulation within the tumor cell nuclei. Technological advances in molecular and genetics will develop tools necessary to manipulate the cell nuclear DNA and target cancer cell.

Resumen

Desde el descubrimiento hace ya mas de veinte años de genes asociados a malignidades, se ha probado que el Cáncer es una enfermedad genéticamente determinada. Múltiples alteraciones genéticas que alteran el curso de división celular son necesaria para que una célula o grupo de células trabajen de forma autónoma y se desarrolle un nuevo crecimiento maligno. La transformación genética de genes reguladores positivos del desarrollo y división celular (conocidos como oncogenes) y la inactivación de genes reguladores negativos del desarrollo y división celular (conocidos como genes supresores de tumores) se combinan para expresar un fenotipo maligno. Estas alteraciones genéticas ocurren producto de traslocaciones, deleciones, inversiones, amplificación o mutaciones especificas del material genético de la célula.

El objetivo de esta monografía es introducir conceptos básicos de biología clínica molecular, describir los hallazgos de genética de los mas importantes tumores sólidos en niños incluyendo el Neuroblastoma, el tumor de Wilms, y el Rabdomiosarcoma. Es responsabilidad del cirujano que maneja tumores sólidos en niños aprender conceptos básicos de genética molecular y biología de tumores para proveer cuidado racional integrado de forma adecuada.

La identificación de nuevos oncogenes y genes supresores de tumores continuará siendo un hallazgo importante en lo que respecta diagnóstico, la detección temprana del Cáncer, su recidiva luego de terapia adecuada y como objetivo potencial para terapia genética. Las proteínas producto de estas mutaciones genéticas son antígenos específicos de tumores y

objetos potenciales de terapia. El problema es que se necesita manipular su desarrollo y división dentro del núcleo de la célula que contiene un sistema estable de división y crecimiento. Es muy probable que avances en genética y biología molecular estableceran las técnicas necesarias para manipular el material genético del ADN y la célula cancerosa afectada en un futuro cercano.

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Artículos de Revisión:

The Withholding and Withdrawal of Medical Treatment: Moral Principles and the Law

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Summary:

In most hospitals in Puerto Rico the dying process of terminally ill patients is inappropriately prolonged. And this occurs often without the patient's consent and in violation of basic ethical principles. Three erroneous beliefs are prevalent: 1-That withdrawing life support therapy is morally or legally different from not starting it. 2-That there is a moral and legal difference between appropriate acts and appropriate omissions. 3-That good medical practice is determined by the courts instead of the medical profession. Institutional policies are not in harmony with contemporary medical ethics. To avoid possible legal entanglements medical institutions permit their faculties to prolong the suffering of patients in violation of two basic moral principles: nonmaleficence and respect for autonomy. An illustrative case provides a philosopher and a moral theologian the opportunity to analyze the applicable moral principles. A professor of jurisprudence reviews statutes evolved at the State and Federal level that support the rights of patients and their families to refuse unwanted treatments. Medical faculties must ensure that institutional policies do not violate their professional ethics. The medical profession and the citizenry at large should lobby for the passage of statutes in Puerto Rico which clearly validate the necessary harmony between medical ethics and the law.

Key words: medical ethics, life support care, terminal care, medical futility, nonmaleficence, respect for autonomy, distributive justice,

Morality is a public system that guides the behavior of rational people. It is a system constantly used in our day–to–day decisions. When stripped of legal fears or odd religious fanaticism, all of us, even in our pluralistic society, should have a sufficient understanding of morality to judge whether a proposed act is immoral in the medical setting or in our daily lives(1).

The social commitments of the physician–to sustain life and relieve suffering–exist within this public moral system. When these two fundamental duties appear to be in conflict, physicians must choose the correct moral act: the action or inaction that best serves the interest of the patient. If the patient is competent, his personal preference should prevail. If the patient is incompetent, and his preferences have not been previously indicated, a surrogate should be identified. "The decision should be based on the best interests of the patient (what outcome would most likely promote the patient's well–being)"(2).

We present here an example of what to our knowledge is a daily occurrence in most of the hospitals of Puerto Rico: the inappropriate prolongation of the dying process of patients, without their consent and in violation of basic ethical principles. The case is discussed by a moral philosopher (JRE), a moral theologian(JF), and a retired surgeon and professor of jurisprudence (RI).

Case presentation

A concerned niece brought to the emergency department a 71– year

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old widower who had suffered from recurrent nausea and vomiting for the last three days and had recently vomited coffee ground material. He had consumed one bottle of rum and smoked three packs of cigarettes daily for the last 50 years. He had moved back to Puerto Rico two months before. His niece had noted a progressive distention of his abdomen in the past 3 weeks. He had been somnolent, disoriented and aggressive for the last two weeks, and had stopped drinking alcohol for the last three days.

On admission to the hospital his temperature was 37.5 C, pulse 106, respiratory rate 28 and blood pressure 140/70 mm of Hg. He appeared chronically ill, jaundiced, and was confused as to time and place. His mouth was missing many teeth and the remaining showed multiple cavities. There was no jugular venous distention. The heart had a regular rhythm and there were no murmurs or gallops. There were basilar crackles bilaterally but no wheezing. The abdomen was markedly distended with fluid and there was venous collateral circulation. The rectal exam showed black stools, positive for blood. There was generalized pitting edema on lower extremities up to the groin and the testicular sac was distended with fluid.

A gastric aspirate was positive for blood and a paracentesis yielded 1500 ml of slightly turbid straw–colored fluid. The patient received thiamine 100 mg IV for the suspected alcohol withdrawal; vasopressin 100 units in 250 ml of DW at 40 ml per hour, and a nitroglycerin infusion 50 mg in 250 ml of DW at 3 ml per hour, as part of the treatment for upper gastrointestinal bleeding; vitamin K 10–mg daily to improve the activity of coagulating factors; furosemide 40 mg every 6 hours and spironolactone 100 mg every 12 hours to reduce edema; ranitidine hydrochloride 300 mg in 100 ml of 0.45 ml per hr. to raise the intragastric pH; lactulose 50 ml every 6 hours to reduce the level of ammonia.

The admission hemoglobin was 10 GM /dl. The only relative with him, his niece, gladly gave the necessary permissions for the blood transfusions and three units of blood were requested. Twenty–four hours after admission he had a cardiorespiratory arrest that required a prolonged cardiopulmonary resuscitation. The patient was placed on mechanical ventilation and telemetry.

The chest film after intubation showed a pulmonary infiltrate on the left lung. A CT of the abdomen showed a left pleural effusion. There was severe distention of the colon with huge amounts of retained fecal material suggesting paralytic ileus and a very large amount of ascitic fluid. The kidneys, liver and spleen were found normal in size.

The second day of hospitalization the patient was seen on consultation by a pneumologist who thought the patient had septic shock and metabolic encephalopathy and dopamine was initiated to keep the blood pressure above 90/60 mm Hg.

On the third day of hospitalization the patient was unresponsive and renal insufficiency worsened. The creatinine increased to 3.5mg / dl and the ammonia levels reached 174 mmol / l. The sputum culture was reported positive for Klebsiella Pneumonia and the ascitic fluid positive for E. Coli. To treat these organisms aztreonam, 1 GM every 8 hours and piperacillin–tazobactam 2.275 mg every 6 hours were added to the intravenous antibiotic regimen. Three units of packed cells were given to maintain the hemoglobin above 10 GM /dl. An increasing amount of dopamine by infusion was required to maintain a physiologic blood pressure. His Glasgow coma index was 3 to 4 with preserved corneal and deep tendon reflexes. The neurologist recommended a head CT scan, that showed mild cerebral atrophy and an electroencephalogram (e.e.g.) which, at the time, was not available in the institution.

At this juncture, three days after admission, a daughter and a son, who had arrived from New York, and the niece of the patient, were told about the progressive multi-organ failure and poor prognosis of the patient. On the fifth hospital day, the daughter, who worked in a hospital, after consulting with her siblings and her cousin, signed a DNR. She informed the staff that her father had told her he did not want ever to be intubated, under any circumstance. That same day the family drafted and signed a paper specifying that it was their unanimous opinion that no further medical interventions be made, including venipunctures. They requested that all treatments, including intravenous infusions, be stopped, fully aware that the patient's biological persistence was dependent on many of the medications and specifically on the mechanical ventilation.

Multiple consultations with senior residents and staff yielded the same answer: "In this hospital, once a patient is placed in a respirator, ventilator support may not be withdrawn. In addition arterial and venous punctures are necessary to monitor the hemoglobin and the level of oxygenation. Intravenous antibiotics and mechanical ventilation must be maintained". An attending physician admitted to the resident that he knew the

prognosis of the patient was zero, but that legal counsel was of the opinion that without a court order a respirator could not be discontinued. He suggested that the Ethics Committee be consulted.

On the sixth hospital day the Ethics Committee was consulted and two days later the committee met with the family. The family brought with them a notarized document requesting that "no artificial measures or mechanisms be used, including the mechanical ventilator. They relieved the Hospital and all the attending physicians of the natural consequences that the disconnection of the mechanical ventilator would bring about".
The committee advised the family that ethically there was no contraindication to discontinue the ventilator, but that it was not legally possible if cerebral death had not been established. The family tried, then, to obtain a court order that would make possible for the medical staff to accept their wishes, but this was not possible. The district attorney informed the family that if the patient was brain dead no court order was necessary and otherwise this was a decision to be made by the physician and the family.
The attending physician, guided by the opinions of legal advisors and the hospital administration, refused to take the responsibility of discontinuing the respirator.
On the ninth hospital day, to the enormous relief of the distressed family, the patient's heart stopped beating. At the time of his demise he occupied a regular hospital bed since the medical staff, conscious that the patient was dying, did not admit him to the overtaxed intensive care unit. From the fifth hospital day when both the family and the staff agreed that further medical interventions were futile, the treatment of this dying patient cost in antibiotics alone over $1300.

Discussion

José R Echevarría Ph.D:

This case dramatizes how clinical judgements not based on sound ethics and legal precedent translate into bad medical practice. It also shows the discrepancy between what we in the medical humanities present to medical students as a patient–centered professional conduct that is both morally and legally defensible, and the "practical" lessons these students later receive in the hospital on how to manipulate patients to shun real or imagined legal entanglements.

A hospital policy which does not allow ventilatory support to be withdrawn when it is no longer medically indicated is ethically obtuse on two counts: It tramples on the right of patients and surrogates to request discontinuation of therapy, and it scares away physicians from trying a potentially useful therapy for fear of later not being able to stop treatment if it proves unsuccessful.

Three erroneous beliefs are at the bottom of the dismaying management of this case. A first error is the assumption that withdrawing life support therapy is morally or legally different from not starting it. Any introductory textbook on medical bioethics will explain that the distinction between withholding and withdrawing is morally irrelevant (3,4). Treatment decisions should be based on the patient's choice and well being, and ultimately on the benefits–burden ratio of the treatment as judged by the individual patients or their responsible decision–makers. Beauchamp and Childress aptly summarize the point: "Treatment can always permissibly be withdrawn if it permissibly can be withheld"(3). Neither does the law attach to the distinction much significance.
The influential and often quoted President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research stated in its now classic report of 1983 that "nothing in the law, certainly not in the context of the doctor–patient relationship makes, stopping treatment a more serious legal issue than not starting treatment. In fact, not starting treatment that might be in the patient's interests is more likely to be held a civil or criminal wrong than stopping the same treatment when it has proved to be unavailing"(5).
A Massachusetts court clearly phrased the point: "a physician has no duty to continue treatment once it has proven ineffective"(6).

It is worth noting that in the case at hand the decision not to withdraw the respirator had nothing to do with suiting the interests of the patient.
It was well understood that the patient's condition could not improve and would soon be fatal.
Why, then, were futile, highly invasive procedures forced on him against the reasonable, rightful and unanimous request of those morally and legally responsible for his treatment decisions? Why was this dying patient held under medical arrest? The answer is simple: the hospital wanted to play safe, taking no risk in actions that could even remotely suggest legal liability.

Underlying this fear is a second mistake: the belief that there is a moral and legal difference between acts and omissions. That mistake explains why the hospital was receptive to the request of the patient's relatives for a DNR order, yet balked at removing the respirator. Not performing CPR if the patient had a cardiorespiratory arrest–the hospital staff confidently thought– would be omitting treatment, for which, upon the patient's death, no one would be found at fault; disconnecting the respirator, however, would be acting

in a way that could result in death (and, reading their minds, in headaches for the hospital!) Yet writing a DNR order is doing something, not just doing nothing. The subtle difference between acts and omissions is philosophically elusive; it does not determine by itself what is morally acceptable. Treatment decisions which allow death to occur, when made by a patient or surrogate, are usually morally acceptable and in compliance with homicide laws (5). During the last two decades United States courts have consistently held that when acts of forgoing life sustaining treatment eventuate in death, the cause of death is not the action of the physician, patient or surrogate, but an underlying disease or injury (8).

The third mistake was to think that since no statute in Puerto Rico explicitly authorizes withdrawing a respirator from a patient, albeit near death, the hospital staff could not proceed with disconnection without a court order. It was assumed that since the legal definition of brain death would allow the withdrawal of the respirator from certain artificially breathing bodies–those certified as brain dead–respirators may not be legally withdrawn from breathing patients unless they are brain–dead. This "legal concern", based on faulty reasoning, diverted attention from the real issue facing the hospital– the moral duty to stop further medical interventions expressly refused by legally responsible relatives–to a non–issue: whether or not the patient was brain–dead. Being legally dead is one reason for ending treatment; another reason, morally binding on caregivers, is valid treatment refusals by patients or surrogates. There is no statute that forbids honoring valid treatment refusals by patients or surrogates. The core of good medical practice is the patient and his needs.

Caregivers in this case, uncritically yielding to a self–serving hospital policy unreasonably designed to ensure absolute immunity, abdicated their duty of loyalty to their patient and respect for his autonomy and dignity.

Jorge Ferrer SJ, STD:

There are families and health care professionals who think that they have the moral duty to use every possible technological intervention in order to extend a dying person's biological life, even if such a life is extremely burdensome for the patient and her loved ones. According to this viewpoint, physical life has to be extended at all costs; death is seen as a medical failure rather than a fact of life, inherent to our finite condition.

As a Christian ethicist, I must strongly disagree with such idolatry of biological life. As R.A. McCormick has pointed out, "the Judeo–Christian tradition has attempted to walk a middle path between medical vitalism (that preserves life at any cost) and medical pessimism (that kills when life seems frustrating, burdensome, "useless") (10). The Judeo–Christian middle course holds that life is a precious good, but not an absolute one. There are other values that may take precedence over the preservation of purely biological life, such as fidelity to God and to one's own moral integrity, the service to loved ones, or the preservation of freedom and peace for one's own nation. Indeed it could be argued that biological life is precious precisely because it allows us to realize the higher spiritual values that give full meaning to human life.

The obligation to preserve biological life has been traditionally understood by Christian theologians as a limited one. This conviction was captured in Roman Catholic theology in the classical distinction between ordinary and extraordinary means. Catholic theologians today have generally abandoned that distinction for it is perceived, among other reasons, as being inappropriately centered on the therapeutic means, rather than on the person. Many contemporary theologians, as well as some official church documents, prefer the distinction between proportionate and disproportionate means to sustain life. Means to sustain life are considered morally obligatory only when the burdens they impose on the patient are proportional to their potential benefits.

Catholic principles are in harmony with contemporary Bioethics and Biolaw. The patient has the right to accept or refuse medical treatments, according to his or her personal values, convictions, projects and preferences. The right to refuse medical treatments includes the withdrawal of treatments already initiated. There is no relevant moral distinction between withholding a treatment (i.e. not initiating it) and withdrawing the same treatment once it has proven to be futile or the competent patient rejects it for personal reasons (for example, stopping a course of chemotherapy because its side effects have become too burdensome for the patient).

In the case under consideration, the patient was not capacitated to express personally his own wishes, but his appropriate representatives repeatedly expressed the desire to have a futile life–supporting intervention withdrawn. The patient's children drafted and signed documents, including notarized documents, expressing their wishes and relieving the hospital from all legal responsibility. It was medically clear that the patient was hopelessly

ill. The mechanical ventilator was not improving the patient's quality of life. The only reason to refuse to comply with the family's request was the practice of defensive medicine. Futile and burdensome treatment was imposed on this patient against the expressed and documented wishes of his legitimate representatives.

At least three basic ethical principles have been grossly violated in this case: nonmaleficence, respect for autonomy, and distributive justice. The violation of the first two principles should be evident from what has been already said. The third one refers to the wasteful use of expensive and scarce technologies to impose on an unwilling patient a clearly futile treatment. Moreover, this case points to a problem of organizational ethics. The administrators of medical institutions are failing in their responsibility to establish and actualize procedures for the ethical management of end–of–life cases.

Ramón Isales, MD, JD:

First let us state the legal problem: Do relatives have the right to refuse treatment for an incompetent patient who has left no documented advance directives?

At the present time there is no law in Puerto Rico that authorizes relatives of an incompetent patient in a terminal condition or a persistent vegetative state to act as a surrogate for this type of patient. Since 1991 four different bills addressing this problem have been filed in the state legislature, but none of them has gone beyond discussion in a legislative committee. By way of contrast, numerous states have approved statutes allowing family members and, in some cases, close friends, to make health care decisions for their relatives in circumstances such as the one described here.

Since the well–publicized case of Karen Quinlan (12) the courts have adopted the doctrine of substituted judgement to solve these cases when there is controversy.
The courts, throughout all jurisdictions, have established that an incompetent patient does not lose his right of autonomy. In the light of this substantive principle, plus the also substantive principle of beneficence, the courts try to determine what the patient would have done if he had been able to express his will.

The Illinois Court, in In re: Estate of Longeway (13), expressed one of the best expositions of the doctrine of substituted judgement when it said: "under substituted judgement a surrogate decision maker makes attempts to establish, with as much accuracy as possible, what decision the patient would make if he were competent to do so. Employing this theory, the surrogate first tries to determine if the patient had expressed explicit intent regarding this type of medical treatment prior to becoming incompetent. Where no clear intent exists the patient's personal value system must guide the surrogate." This decision evidences a clear determination of the courts to protect the patient's wishes and to protect his personal dignity and right of autonomy.

In the case of Karen Quinlan the New Jersey Court said (12): "We consider that a practice of applying to a court to confirm such decisions (of a hospital ethics committee) would generally be inappropriate, not only because that would be a gratuitous encroachment upon the medical profession's field, but because it would be impossibly cumbersome". Later on in the decision it added: "Decision making within health care, if it is considered as an expression of a primary obligation of the physician, primun non nocere, should be controlled primarily within the patient–doctor–family relationship." This expression has found echo in other jurisdictions.

We know that no right is absolute. The Massachusetts Supreme Judicial Court, in the case of Belchertown State School versus Saikewicz, found four countervailing state interests that could overcome a patient's or a relative's choice(14): 1- preservation of life, 2- protection of the interests of innocent third parties, 3- prevention of suicide, 4- maintenance of the ethical integrity of the medical profession. In the case at hand none of those interests were menaced.

In the Belchertown case the Massachusetts Court further added (14): "It is clear that the most significant of the asserted state interests is that of the preservation of human life. Recognition of such an interest, however, does not necessarily resolve the problem where the affliction or disease clearly indicates that life will soon end, and inevitably be extinguished. The interest of the state in prolonging a life must be reconciled with the interest of an individual to reject the traumatic cost of that prolongation". This doctrine has been universally approved in the United States.

Moreover, a constitutionally protected liberty interest in refusing unwanted medical treatment has been recognized by the Supreme Court of the United States in the case of Cruzan versus Director of Missouri Department of Health (15). When a relative refuses treatment the state may require clear and convincing evidence that such was the wish of the patient. But, once that clear evidence is presented, as it was in the case under discussion, the patient's wishes as expressed by his relatives should be respected without the need of a court order. Supreme Court Judge O'Connor

expressed it this way: "In my view such a duty may be constitutionally required to protect the patient's liberty interest in refusing medical treatment".

Do relatives have the right to refuse treatment for an incompetent patient who has left no documented advanced directives? In light of the above, it is my opinion that the answer is a definite yes.

Conclusions

Statutory regulation is not a requirement for action in the medical environment. Courts have traditionally paid deference to medical actions performed in good conscience and in accordance with the standards of the profession. Most of the fears of legal entanglements on the part of health professionals and hospitals in cases where withdrawal of futile treatment is the appropriate medical and moral action are not justified.

Medical faculties most ensure that institutional policies do not violate their professional ethics. Administrators must be made aware of the right of patients and their surrogates to request humane withdrawal of futile medical treatments, including ventilators. Futile treatments, particularly when they are unauthorized, are unethical and may be subject to challenge in a court of law. The medical profession, hospital administrators and the citizenry at large (as has occurred in other jurisdictions) should actively lobby the legislature for passage of statutes that validate the necessary harmony between medical ethics and the law.

Resumen:

En la mayoría de los hospitales de Puerto Rico el proceso de morir de pacientes en fase terminal es inapropiadamente prolongado. Y esta prolongación inapropiada ocurre frecuentemente sin el consentimiento del paciente y en violación de principios éticos básicos. Hay tres creencias erróneas comunes: 1- Que retirar la terapia de sostén es moralmente o legalmente diferente a no iniciarla. 2- Que hay una diferencia moral y legal entre acciones apropiadas y omisiones apropiadas. 3- Que la práctica correcta de la medicina la determinan los tribunales y no la profesión médica. La política de las instituciones hospitalarias no armoniza con los principios de ética médica contemporáneos. Para evitar posibles complicaciones legales, las instituciones hospitalarias permiten la prolongación del sufrimiento de pacientes en violación de dos principios morales básicos: no–maleficencia y el respeto a la autonomía. Un caso ilustrativo permite a un filósofo y a un teólogo moral analizar los principios morales violados. Un profesor de derecho revisa la evolución de la jurisprudencia estatal y federal que sostiene el derecho de pacientes y de sus familias a rechazar tratamientos no deseados. Las facultades médicas de instituciones hospitalarias deben asegurarse de que la política institucional no viola la ética profesional. La profesión médica y la ciudadanía en general deben exigir de la legislatura de Puerto Rico la aprobación de estatutos que claramente establezcan la necesaria armonía entre la ética médica y la ley.

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Reporte de Caso:

Unusual Clinical Presentation of a Prenatally Diagnosed Intracardiac Tumor in an Asymptomatic Newborn with Spontaneous Regression During Infancy

J. Bauza-Rossi, MD, H. Tosson, MD

Introduction:

Primary tumors of the heart are uncommon in infancy and childhood. (1) When present, depending on their location, size, and time of onset, they can lead to hemodynamic compromise and arrhythmias resulting in a fatal outcome before or after birth. (2) Although prenatal ultrasonography allows for a high rate of detection, diagnosis of cardiac tumors is usually made after birth in symptomatic infants who present with a heart mumur, heart failure, cyanosis, or arrhythmia. (3, 4)

Most primary cardiac tumors detected prenatally and at birth are rhabdomyomas. (5, 6) Spontaneous regression of these lesions has been previously reported. (13) These tumors are found in at least 50% of patients with Tuberous Sclerosis. (8, 11) Thus, patients with cardiac rhabdomyomas must undergo work up to rule out the presence of Tuberous Sclerosis. However, during early infancy, in the absence of family history positive for this disease, the tumor itself may be the only manifestation of Tuberous Sclerosis.

We report the spontaneous regression of a prenatally diagnosed intracavitary tumor that partially filled the right ventricle without obstruction of either the inflow or the outflow, identified through routine prenatal ultrasonography in an asymptomatic infant. The tumor disappeared spontaneously and completely over 7 months of observation. The patient remained tumor-free and asymptomatic by the first birthday.

This case illustrates the usefulness of routine prenatal ultrasonography, the benefits of echo-doppler as a tool for serial assessment of the tumor structure and intracardiac hemodynamics, and the option of abstaining from surgical excision when tumors with the potential for spontaneous regression do not interfere with intracardiac hemodynamics nor are a cause of life-threatening arrhythmias.

Key words:
Intracardiac tumor, rhabdomyoma, tuberous sclerosis, asymptomatic infant, prenatal ultrasonography, 2-D echocardiography, cine image digital memory, B-Color, Color Doppler.

Case Report:

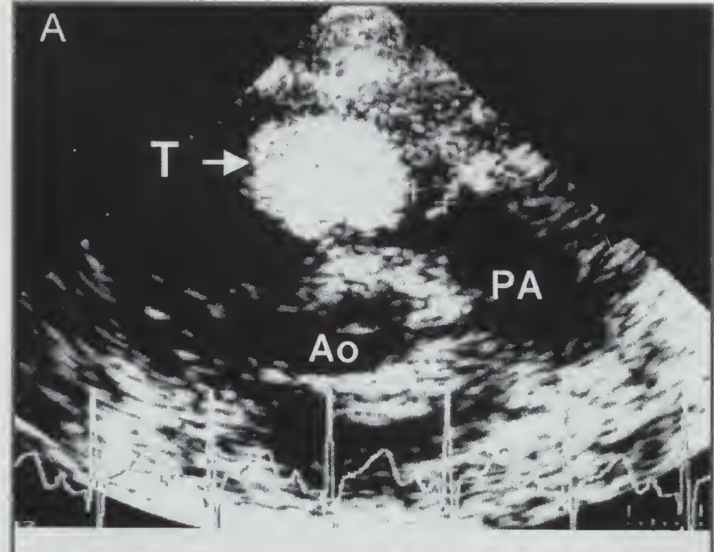
The patient was an asymptomatic full term male infant born at the Bayamón Regional Hospital to a healthy 20 year-old gravida 2, para 2, woman by spontaneous vaginal delivery after an uncomplicated gestation. Birth weight was 3900g. Apgar score was 8 and 9 at 1 and 5 minutes respectively. The parents and one sibling were healthy. There was no family history of neurological disease, seizure disorder, mental retardation, or Tuberous Sclerosis.

A highly echogenic, round, intracardiac mass was found on routine fetal sonogram at 18 weeks gestation. There was never evidence of fetal distress, arrhythmia, or nonimmune hydrops on subsequent fetal studies. Physical examination at birth revealed a well developed, healthy-looking boy without heart murmurs, or unusual heart sounds. Peripheral pulsations were normal. There were no visible skin lesions nor hypomelanotic macules that were discernible by ultraviolet light examination (Wood's light). Skull series, electroencephalogram, and Cranial Computerized Tomography were normal. The electrocardiogram was normal for age without evidence of arrhythmia, strain pattern, undue hypertrophy, heart block, or pre-excitation. The chest radiograph showed a normal cardiovascular silhouette with normal pulmonary circulation.

A two-dimensional echocardiogram obtained at birth located the prenatally detected intracavitary mass within the right ventricular chamber. Upon parasternal short axis interrogation at the level of the aortic annulus, an ellipsoid shaped mass was seen within the right ventricular body, midway between the tricuspid and pulmonary valves,

but closer to the latter. (Fig. 1A) The tumor was initially 1.9 x 1.2 cm with a cross-sectional area of 2 cm2. It was attached to the right ventricular free wall by a stem that was 0.6 cm long and 0.4 cm wide. This stem allowed for a restricted range of motion within the chamber during the cardiac cycle along both the long and short axis of the right ventricle. (Fig. 1B) This caused the mass to apparently shrink and increase its size as it moved sideways from and towards the scanning plane.

B-Color processing of the two-dimensional gray scale image identified the intracavitary mass as being well circumscribed, finely speckled, of homogeneous texture, and isoechoic with the surrounding myocardium. (Fig. 2) Spectral Doppler analysis of right ventricular hemodynamics revealed no signicant gradients across the right ventricular outflow tract, no evidence of Tricuspid stenosis, and no significant tricuspid backflow. Color Doppler mapping allowed for identification of the hemodynamics around the floating tumor and the resulting tumor-eclipse-effect caused by the Color-coded blood as it passed by the mass during the cardiac cycle. (Fig. 3) The patient remained asymptomatic throughout his first year. Serial two-dimensional echocardiography documented the reduction of the tumor mass at a rate of 3 mm per month until it completely disappeared by age 7 months. (Fig. 4) On his first birthday, the patient remained asymptomatic and tumor free.



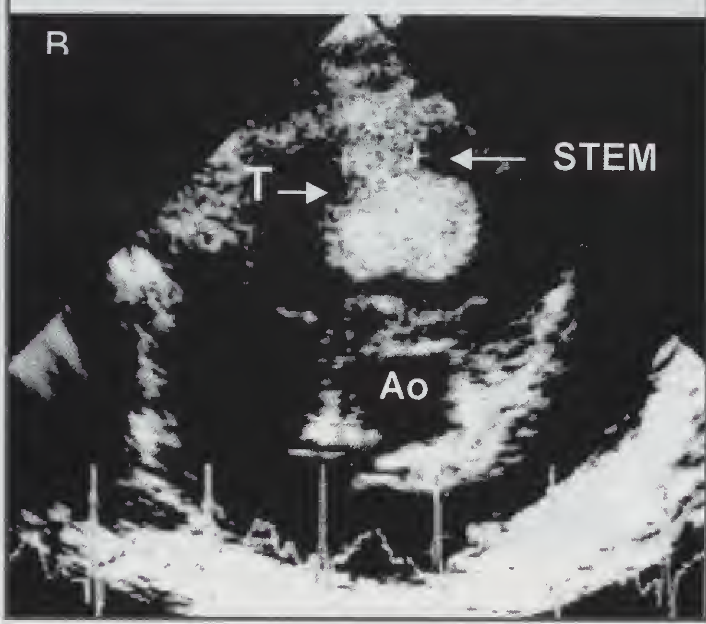


Figure 1. Two-dimensiotal echocardiogram of patient at age 1 month. Parasternal short-axis in: (A) Diastole and (B) Systole. In diastole the free-floating intracavitary right ventricular tumor moves towards the scanning plane so that it appears to occupy the entire right ventricular outflow tract. In systole the tumor moves away from the scanning plane so that its attachment to the right ventricular free wall is revealed. T, Tumor; Ao, Aorta; PA, Pulmonary Artery.

Discussion:

Primary cardiac tumors are uncommon at all ages, but they are least common among infants. (3, 8) In a 1968 report of 11,000 pediatric autopsies, the incidence of cardiac tumors was determined to be 0.027% (1). Rhabdomyomas, fibromas, myxomas, hemangiomas, and teratomas are, in decreasing order of frequency, the most common benign primary cardiac tumors in childhood. With the exception of rhabdomyomas that are frequently multiple, all other benign primary cardiac tumors appear as solitary lesions. (3, 9)

By far, rhabdomyomas are the most frequently encountered cardiac tumors in childhood. Most cases have been presented below one year of age and the male/female ratio of incidence is reported to be 2:1. (5, 10, 11) Rhabdomyomas are well circumscribed, non-encapsulated, usually intramural nodules which when large enough can protrude into the cardiac chambers. When intracavitary, these tumors can be broad based or attached to the myocardial wall by a short stalk. They can occur anywhere in the heart with the left ventricle followed by the right ventricle being the preferred locations. (4, 6)

Depending on their size and location, rhabdomyomas can interfere with cardiac function causing heart failure, hypoxemia/ cyanosis, life-threatening arrhythmia, and death before or after birth.

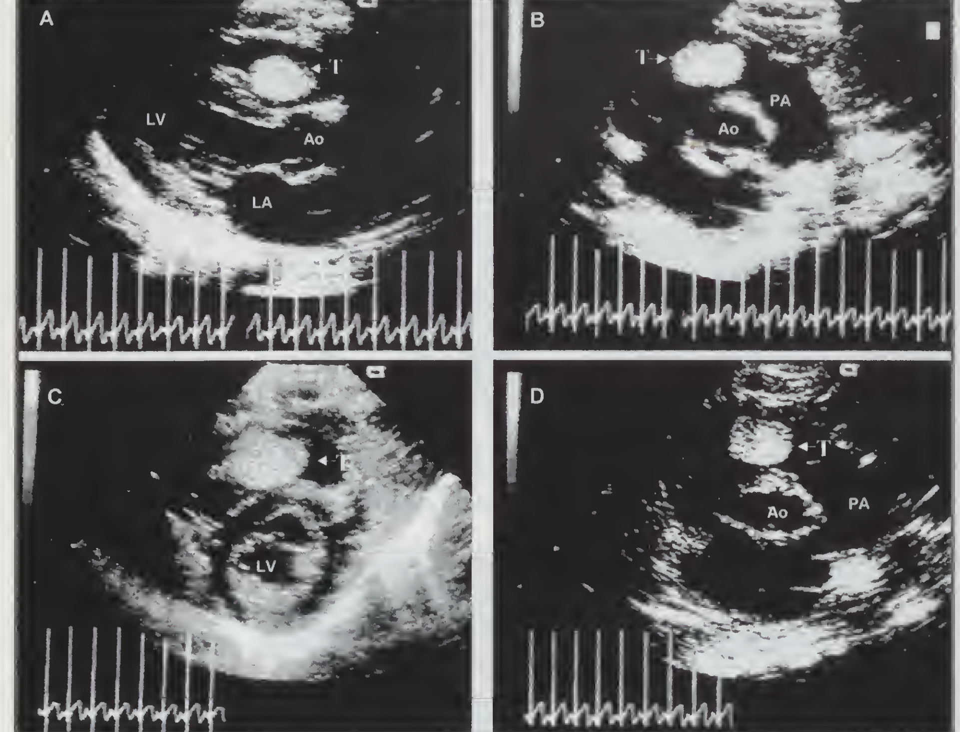


Figure 2.
B-color maps of two-dimensional echocardiographic views of patient at age 2 months. (A) Parasternal long-axis in Systole. (B) Parasternal short-axis in Systole. (C) Parasternal short-axis at the level of the mitral orifice showing the tumor attachment to the right ventricular wall. (D) Parasternal short-axis in diastole.
T, Tumor; LV, Left Ventricle; Ao, Aorta; PA, Pulmonary Artery; LA, Left Atrium.

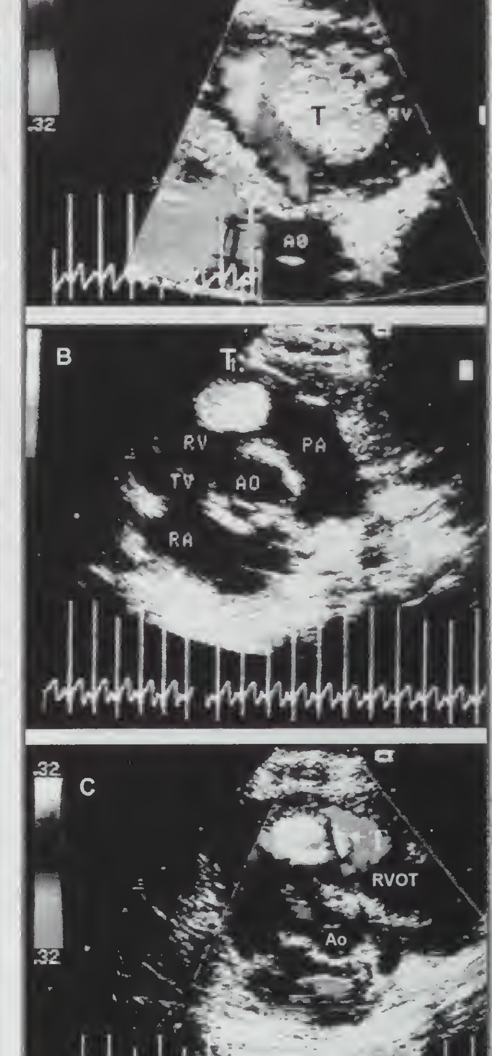


Figura 3.
Two-dimensional echocardiographic views of patient at age 2 months utilizing simultaneous B-Color maps and Color Doppler. (A) Modified apical 5 chamber view during diastole reveals a jet of color-coded tricuspid inflow-blood passing between the ventricular septum and the anteriorly attached right ventricular tumor. (B) Parasternal short-axis view in systole. (C) Modified parasternal short-axis view in diastole of the right ventricular tumor as it is eclipsed by Color-coded diastolic flow passing towards and away from the tumor.
T, Tumor; RV, Right Ventricle; RA, Right Atrium; RVOT, Right Ventricular Outflow Tract; PA, Pulmonary Artery; Ao, Aorta.

Nonimmunogenic hydrops can be due to both hemodynamic compromise and to arrhythmia. (2, 20-22)

After birth, rhabdomyomas can cause valvular obstruction mimicking atrio-ventricular valve atresia and semilunar valve stenosis. (23-25) Several arrhythmias such as Supraventricular tachycardia, Ventricular tachycardia, Ventricular fibrillation, and the Wolff-Parkinson-White Syndrome have been recognized as complications of intracardiac rhabdomyomas. (26-29)

The association between intracardiac rhabdomyomas and Tuberous Sclerosis has long been established. (6, 8, 10-12, 17, 30) The disease is a hamartosis where an abnormal mixture of tissue with tumor-like excesses develop in multiple visceral organs. At least 50% of patients with intracardiac rhabdomyomas have Tuberous Sclerosis and vice versa. The risk of patients with rhabdomyomas of having Tuberous Sclerosis increases if tumors are multiple. (6, 11, 17, 23)

Rhabdomyomas are hamartomas or histologically benign lesions that do not progress and that often if not always go into spontaneous regression. (5, 6, 12) Proof of spontaneous regression of these tumors abounds in the literature. (11, 13-19)

A clue to the spontaneously evanescent nature of rhabdomyomas lies in the fact that in Tuberous Sclerosis the incidence of rhabdomyomas is much higher in children than in adults. (12) Because of these characteristics, rhabdomyomas have been recognized as a disease of the young. (17)

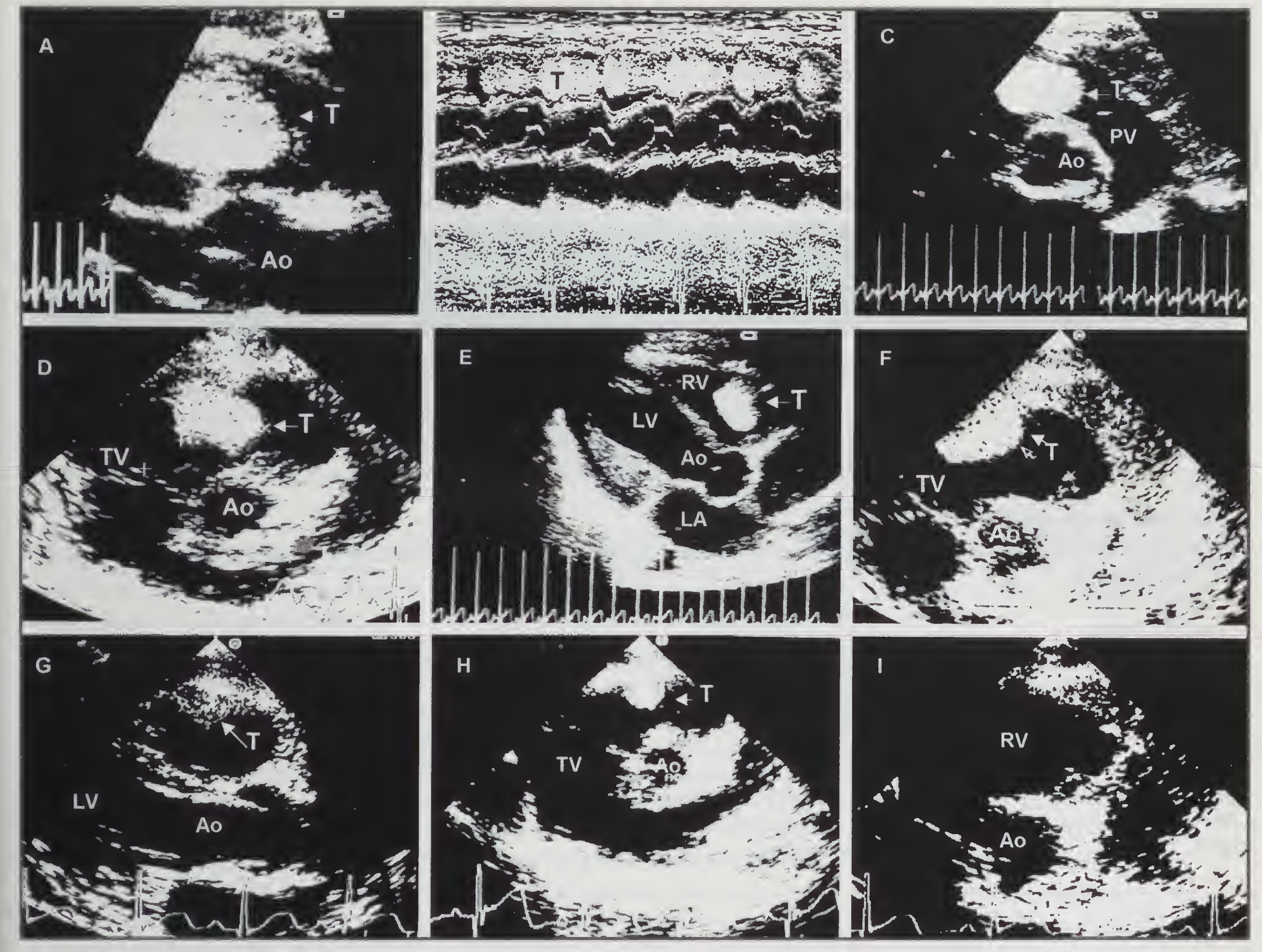


Figure 4.
Assorted two-dimensional echocardiographic views of patient at different ages depicting the progressive regression of the right ventricular tumor. (A) Modified parasternal long-axis view at birth. (B) M-mode strip at the level of the right ventricular outflow tract at birth. (C) Parasternal short-axis view at age 1 month. (D) Parasternal short-axis view at age 2 months. (E) Modified apical 5 chamber view al age 3 months. (F) Parasternal long-axis view at age 4 months. (G) Parasternal long-axis view at age 5 months. (H) Parasternal short-axis view at age of 6 months. (I) Parasternal short-axis view of the tumor-free right ventricular chamber at age 7 months.
T, Tumor; Ao, Aorta; RV, Right Ventricle; PV, Pulmonary Valve; LA, Left Atrium; RA, Right Atrium; TV, Tricuspid Valve; LV, Left Ventricle.

All intracardiac rhabdomyomas causing hemodynamic compromise must undergo surgical excision. However, a watchful conservative approach is desirable in the asymptomatic patient given the possibility of spontaneous regression. In our patient, although the tumor was intracavitary, the distinctly favorable location, midway between the tricuspid and the pulmonary valves, together with the absence of symptoms allowed for this approach. While most infants with intracardiac rhabdomyomas are symptomatic, the lack of symptoms in our case despite the relative large size tumor is unusual. In the asymptomatic infant, the surgical decision must be made anticipating the possible migration of the tumor into either the inflow or outflow of the right ventricle causing occlusion and sudden death. In our patient,, review of the cine loop 2-D image digital memory allowed for a clear perception of the tethered tumor as it shifted back and forth throughout the cardiac cycle without encroaching into neither the inflow or the outflow of the right ventricle. B-color processing of the gray scale 2-D image was helpful in that it allowed for a clearer visualization of the tumor. (7, 31)

Although we did not have histologic confirmation as to the nature of our patient's tumor, its echocardiographic morphology along with the fact that it disappeared spontaneously is

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Núm. Licencia __________ Especialidad: __________ Año Graduación __________

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sufficient proof that this was indeed a rhabdomyoma. Our patient did not have evidence of Tuberous Sclerosis by family history, a history of seizures, an abnormal cranial CAT scan, nor cutaneous lesions. Since about two-thirds of cases of Tuberous Sclerosis are sporadic spontaneous mutations occurring in the absence of a family history for the disease (32); the tumor itself may be at this age the only manifestation of Tuberous Sclerosis. (9) All infants with spontaneously disappearing intracardiac tumors must be watched for the development of Tuberous Sclerosis

In the past, cardiac tumors have been seldom recognized before the infants death, thus early diagnosis is paramount for survival. (4)
Our case represents at 18 weeks the earliest in utero diagnosis by ultrasonography of an intracardiac tumor that went on to disappear spontaneously. This case emphasizes the importance of prenatal ultrasonography with attention to structural heart disease and the benefits of B-color mapping of 2-D echo-doppler images for serial assessment of intracardiac masses with a potential for hemodynamic compromise and/or spontaneous regression.
The conservative approach was justified in our case given the positive outcome.

Introducción:

Los tumores cardiacos primarios son poco frecuentes en la infancia. Cuando están presentes, dependiendo de su localización, tamaño y tiempo de debut, pueden causar compromiso hemodinámico y arritmias, lo que puede resultar en un desenlace fatal antes o después del nacimiento. La ultrasonografía prenatal permite una alta tasa de detección de estos tumores.

Se presenta el caso de un tumor intracavitario que llenaba parcialmente el ventrículo derecho sin causar obstrucción del tracto de entrada o salida de dicho ventrículo el cual se identificó por ultrasonografía prenatal rutinaria en un infante asintomático.

El tumor desapareció en 7 meses de observación de forma espontánea y completa. La estructura del tumor y la hemodinámica intracardiaca se evaluó con procesamiento por Color-B de la imagen bidimensional en escala de gris y por Doppler a color. El paciente se mantuvo libre de tumor y asintomático en su primer año de vida.

La mayoría de los tumores cardiacos primarios detectados prenatalmente son rabdomiomas. Se ha reportado remisión espontánea de estas lesiones previamente. Los rabdomiomas cardiacos se han relacionado con esclerosis tuberosa e incluso pueden ser la primera manifestación de esta enfermedad por eso estos pacientes se deben evaluar para descartarla.

Este caso enfatiza la importancia del cernimiento rutinario por medio de ultrasonografía con atención especial a defectos cardiacos, el beneficio de eco-Doppler como herramienta para la evaluación seriada de tumores intracardiacos y la necesidad de evitar la extirpación quir˙rgica de estos tumores cuando estos muestran un potencial para la remisión espontánea y sobretodo cuando no interfieren con la hemodinámica ni son causa de arritmias malignas.

Acknowledgements:
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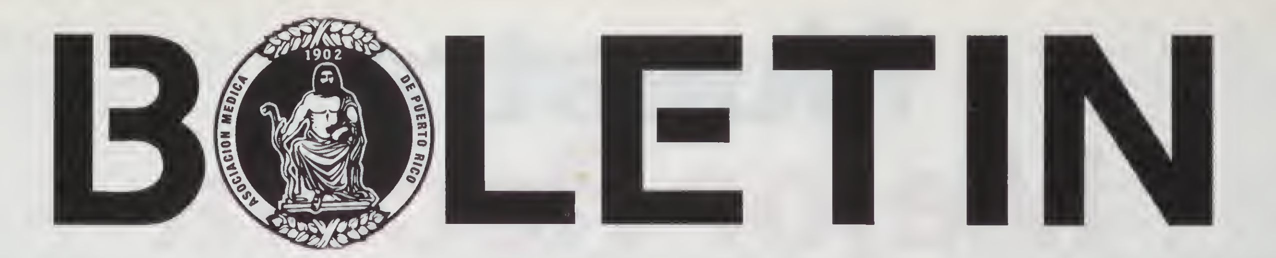
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Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

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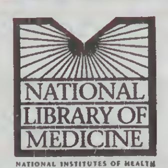
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EDITORIAL

Rosa Pérez Perdomo, MD, PhD

Los especialistas en Otorrinolaringología en Puerto Rico, han realizado una labor de la que pueden sentirse orgullosos. Como se evidencia en los diferentes tópicos cubiertos en esta edición especial existe en este grupo de profesionales un envolvimiento en la enseñanza, la investigación, el servicio y la práctica. Sin embargo, a la vez que esta compilación de artículos tiene como objetivo el difundir las diferentes dimensiones de esta especialidad, nuestra exhortación se dirige hacia las oportunidades y retos que se pueden seguir alcanzando.
La expansión en el área de investigación de muchas de las especialidades en Puerto Rico no solamente es altamente deseada sino una gran necesidad.

Se deben realizar esfuerzos dirigidos a fomentar el desarrollo de la investigación clínica y epidemiológica, que nos permitan obtener información de condiciones específicas en Puerto Rico.
El entrenamiento de los médicos y otros profesionales de la salud debe incluir conocimientos por lo menos básicos, que les capaciten para realizar proyectos de investigación dentro de su especialidad.
Se deben crear incentivos tanto económicos como científicos, que promuevan la participación del médico en actividades de investigación. La creación de un "track" con investigación dentro de las especialidades podría ser una forma de iniciar este estímulo.

Sabemos que no todos los que pasan por una especialidad desearán seguir una carrera dentro de la investigación. Sin embargo, el lograr la participación de unos pocos dentro de este campo será de gran beneficio para la investigación clínica especializada.

Exhortamos a quienes tienen el poder decisional para estos cambios, a que consideren esta visión de futuro como un medio efectivo para aumentar la investigación dentro de las especialidades médicas en Puerto Rico.

MENSAJE

La Sección de Otolaringología Cirugía de Cabeza y Cuello de la Asociación Médica de Puerto Rico, la Sociedad de Otolaringólogos Cirujanos de Cabeza y Cuello de Puerto Rico, el programa de adiestramiento de Otolaringología Cirugía de Cabeza y Cuello, del Recinto de Ciencias Médicas de la Universidad de Puerto Rico se complace en presentar a la clase médica de Puerto Rico esta edición especial del Boletín de la Asociación Médica de Puerto Rico.

Hace varios años que comenzó una preocupación entre la membresía de las diferentes agrupaciones de Otolaringología Cirugía de Cabeza y Cuello en la cual presentían que la especialidad no era bien entendida. Tal vez esta confusión surge del viejo nombre de la especialidad de Oídos Nariz y Garganta, conocido mejor entre la comunidad médica de ENT, pero nuestra especialidad es mucho más abarcadora que meramente oídos, nariz y garganta. El colega Guillermo Martínez lanzó un reto a los miembros de la especialidad a que nos diéramos a la tarea de difundir a la clase médica de Puerto Rico lo que es la Otolaringología Cirugía de Cabeza y Cuello.

Este es el producto de más de dos años de trabajo, una compilación de artículos que en sentido general le da al lector una idea de lo que hace nuestra especialidad y nuestra historia en Puerto Rico.

Esta edición especial del Boletín de la Asociación Médica de Puerto Rico llega a la clase médica de Puerto Rico gracias a una aportación de la firma Glaxo Wellcome de Puerto Rico y su compromiso con la educación médica. Nuestro agradecimiento a la Asociación Médica de Puerto Rico por haber apoyado esta iniciativa. A todos nuestros colegas en Puerto Rico esperamos que el contenido de esta edición del Boletín les sea de beneficio profesional.

Charles Juarbe M.D.
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Puerto Rico.

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Artículos Especiales:

History of Otolaryngology in Puerto Rico 1898 - 1989 (Part 1)

*Antonio Rullán, M.D., FACS**

Puerto Rico was discovered by Christopher Columbus on his second voyage, November 19, 1843. Juan Ponce de León in 1508, established the first capital at Caparra, nearby what is now San Juan. In spite of many attacks by British and by Dutch forces the island remained a Spanish colony until July 25, 1898, when, during the Spanish-American War, troops entered thru Guanica Bay near Yauco. It was a very short war. By the Treaty of Paris on December 10, 1898, Spain ceded Puerto Rico to the U.S.A.

As far as medical history is concerned, the Puerto Rico Medical Assoc. founded September 21, 1902, by Dr. Manuel Quevedo Báez. In 1914, the Puerto Rico Academy of Medicine was established and a Section of Ophthalmology and Otolaryngology was formed under Dr. Manuel Figueroa -the outstanding general surgeon at that time. The Academy lasted only until 1923.

The Section of Ophthalmology and Otolaryngology of the Puerto Rico Medical Association was founded in 1940. On March 31, 1970 it was divided into Ophthalmology and Otolaryngology sections.

The University of Puerto Rico was established November 12, 1903. Later the School of Tropical Medicine, in conjunction with Columbia University of New York City, was established in 1925.

On December 8, 1941 the United States entered the Second World War which ended with Japan's surrender on Sept. 18, 1945. Most of our younger physicians served in the Armed Forces of our nation.

Many things changed for the best after the war The School of Medicine of the University of Puerto Rico initiated its first class on August 1950 and graduated 45 physicians on June 1954. The Residency training program in Otolaryngology was started July 1, 1959 by Dr. José Picó at the San Juan City Hospital. The first two residents finished in 1962 The program was taken over by the University of Puerto Rico School of Medicine on July 1970. Up to June 30, 1989, fifty eight physicians have finished their training in this program. Of these, 18 have been certified by the American Board of Otolaryngology.

When Dr. José Picó retired in 1974, Dr. Antonio Rullán took over as Full Professor and Director of the program. When Dr. A. Rullán retired in 1978, Dr. Juan Trinidad took over the position which he still holds. The first two months of the Residency Training Program are spent taking the Basic Course (40 hours weekly) at the University of Iowa under Dr. Brian F. McCabe. Starting September 1989, there will be an interchange of Residence with the University of Buffalo, N.Y., for a period of three months for each resident.

Other historical events that have changed the practice of Otolaryngology in Puerto Rico have been:

1. The discovery of Penicillin by Sir Alexander Fleming in 1938 at St. Mary's Hospital, London, England. Withthe possible elimination of many infectious diseases they used to say "ENT is a dying specialty". Insted a far new expansion of the specialty occured, and Head and Neck and Plastic surgery have become part of our field since 1948. On June 11, 1948, the first total laryngectomy combined with resection of the right pyriform sinus and upper portion of the esophagous, was done in Puerto Rico by Drs. David Rodríguez Pérez and José Picó at the Oncologic Hospital of San Juan.

2. The Hill-Burton act helped finance construction of many governmental and private hospitals offering the surgeon an excellent place to practice surgery.

3. The creation of pre-payment plans such as Blue Cross in 1944 and Triple S (Blue Shield of P.R.) in 1959, as well as Medicare, guaranteed the physician payment for services rendered. Before, most of the physicians depended on a government paid position. The number of private patients was very limited.

4. Air transportation between the island and the mainland made interchange very easy. From an

* Dr. Rullán pass away last year.

8 hours non-stop flight from New York City to San Juan in 1946 it has come down to little over 3 hours (By boat. It used to take three and a half days).

5. Law 11 of June 23, 1976 requires a minimum of 20 credits hours per year in Continued Education for physicians. To renew the license to practice medicine, Law 4 of September 12, 1983 requires renewal every three years, thus 60 credit hours of Continued Medical Education are required.

With these historical data as back-ground, we can divide the practice of Otolaryngology in Puerto Rico into two periods: Period I from 1898 until 1946 and Period II from 1946 until today.

PERIOD I (1898 - 1946)

During this period, Ophthalmology and Otolaryngology were practice in combination. Training was by preceeptoraship. The physician interested in a specialty would take a post-graduate course at the USA or Europe. Course varied from weeks to months. Most Puerto Rican physicians attended the Post-Graduate School of the University of Pennsylvania. They returned home and worked at a government hospital, usually under the guidance of a senior surgeon, which on many occasions was, a General Surgeon. This way they put into practice what they had learned in theory at the post-graduate school. At that time there was no organized residency training program in Puerto Rico.

The physicians practising the specialty during this First period here at San Juan, whom I recall by personally knowing or working with them, were:

Dr. Nicolás Quiñones Jiménez
Dr. Agustín Laugier
Dr. Mariano Caballero
Dr. Miguel A. Mariani
Dr. Adolfo Bernabe
Dr. Frank Quiñones
Dr. Rafael Maldonado

Dr. Lewis Babcock arrived in Puerto Rico from New Jersey after World War I and stayed here until he died of Cancer of the Larynx in 1947.

Dr. Antonio Molina Saint Remy practised in San Juan around 1912 and wrote about Tuberculosis of The Larynx.

I would like to make special mention of the following four Otolaryngologists who were also practising before 1946 and were already certified by the American Board of Otolaryngology:

Dr. Juan H. Font - certified 1933
Dr. Carlos E. Muñoz MacCormick - 1945
Dr. José T. Picó - 1946
Dr. Miguel Alonso - 1946

A short resumes of these four Otolaryngologists follows:

Dr. Juan H. Font

Born in Barranquitas, 1895
Died San Juan November 9, 1988
M.D. from Medical College of Philadelphia 1916
Medical Officer, Army of the United States, 1918 - 1922
Post graduate courses in Otolaryngology at U.S.A. and Vienna, Austria.
Certified by the American Board of Otolaryngology, 1933
President of the Puerto Rico Medical Association, 1936
President Vth Congress of the Pan American Association of Otolaryngology, April 2-6, 1956
Accepted by the Triological Society in 1952 with the Thesis "Jugular Foramen Syndrome: Translent case of Viral Etiology". Archives of ORL 56; 134 - 141 August 1952
Fellow, American College of Surgeons 1951

Dr. Carlos E. Muñoz MacCormick

Born in Caguas, August 27, 1907
M.D. Boston University 1930.
Intern. Boston City Hospital, 1931
General Practice, Arroyo, P.R. 1932 - 1935
Post-Graduate courses in Otolaryngology - at Boston, 1935 - 1938 while
Chief Medical Officer CCC camps 1938 - 1945, Otolaryngology Service, San Juan City Hospital (Chief 1941 - 1944)
1942 - 1945 General Executive Officer, Civilian Defense of P. R.
1944 & 1945 President, P.R. Medical Association
Certified by the American Board of Otolaryngology 1945
Accepted by the Triological Society 1948, Thesis "Esophageal Varices-Sclerosing Injection"
1951 - 1978 Clinical Professor of Otolaryngology, Univ. of Puerto Rico School of Medicine
1971 - 1972 President Pan American Association of Otolaryngology
1956 - 1961 Medical Director, Hospital Auxilio Mutuo, Hato Rey
April 1972 Guest Speaker of the Annual Meeting of the Triological Society held at Palm Beach, Florida
1982 President, XVIII th Congress of the Pan American Association of ORL and B.E. Member: Collegium Otorhinolaryngologium: American Bronchoesophagological Association (1953)
American Laryngological Association
Fellow American College of Surgeon 1951

Dr. José T. Picó Santiago

Born in Coamo, 1909
M.D. University of Maryland - Baltimore 1933
1935 - 1936 Post-Graduate Course in Otolaryngology at the University

of Pennsylvania. From 1939 ENT Service Staff of San Juan City Hospital (Chief 1945 - 1974)
Certified by the American Board of Otolaryngology 1946
Professor of Otolaryngology at the University of Puerto Rico School of Medicine 1952 - 1976
Accepted by the Triological Society, 1966. Fellow American College of Surgeons, 1954
Started the Residency Training Program July 1, 1959 at the San Juan City Hospital.

Dr. Miguel Alonso
Born in Palmer, Puerto Rico
Died San Juan 1966
1945 Fellowship in Otology with Dr. Theodore E. Walsh at Washington University St. Louis, MO
His only two sons: Miguel R. and William A. are both certified Otolaryngologists practising in Tampa, Florida.

PERIOD II

1946 saw the arrival of Otolaryngologists who had received formal residency training in the mainland. The first to arrive was Dr. William Reichard in 1946, who worked at the Veterans Administration Hospital here at San Juan. He had trained at the Graduate Hospital of the University of Pennsylvania. Was certified by the Board in 1949. Died in 1960. Dr. Lorenzo Arusaga arrived in 1959. He also trained at the Graduate Hospital of the University of Pennsylvania. Was certified by the Board in 1956.

At list of all the Otolaryngologists that trained in the mainland and the year they arrived in Puerto Rico follows; all the other practicing otolaryngologist have been train in Puerto Rico since 1962.

OTOLARYNGOLOGISTS WHO TRAINED AT RESIDENCY PROGRAMS IN THE MAINLAND
(In order of the year they arrived at Puerto Rico)

Name	Location of Practice	Residency Program	Years of Residency	Arrived Year	FACS	Year Cert. Bd ORL	Other Int
William Reichard	SJ	Graduate Hasp. Univ. Penn.	1944 - 1946	1946		1949	Died 1960
Larenza Arzuaga	SJ	Graduate Hasp. Univ. Penn.	1947 - 1949	1949		1956	
Jaime Fant	SJ	Graduate Hasp. Univ. Penn.	1943 - 1951	1951			
Antonio Rullán	SJ	NYU-Bellevue Med. Center NYC	1950 - 1952	1952	1954	1954	Tria ABEA 1961 - 1966
Rex Bunker	Caguas	Univ. Syracuse, NY	1954 - 1956	1956	1961	1957	
Enrique Vicens	Pance	Jefferson Univ. Phila.	1953 - 1956	1956	1966	1957	Palitician Sparts
Philip Zetterstrand	SJ	Carnell-NY Hosp.	1960 - 1964	1964		1955	Maved ta NY
Jasé Hernández	Arecibo	NYC Hasp. Queens	1954 - 1957	1957			Daminican
Pabla Guardiala	Mayaguez	Syracuse Univ.	1955 - 1958	1958		1960	
Carlas Rajas	SJ	NYC Hasp. Queens	1958 - 1960				
Hamer Kimmich	SJ	Temple Univ. Phila.	1956 - 1959	1960		1961	Died 1989 at Indiana

TABLA CONTINÚA EN LA PÁG. 100

OTOLARYNGOLOGISTS WHO TRAINED AT RESIDENCY PROGRAMS IN THE MAINLAND
(In order of the year they arrived at Puerto Rico)

Name	Location of Practice	Residency Program	Years of Residency	Arrived Year	FACS	Year Cert. Bd ORL	Other Int
Otto Corretjer	SJ	Temple Univ.	1960 - 1963	1963			
Alexis Fernándz	SJ	Temple Univ.	1961 - 1964	1971			
Arnaldo Pérez Vega	Humacao	Richmons, VA	1962 - 1964	1964			
Andrés Maeso	SJ	Richmond, VA	1962 - 1965	1965			
Luis De Jesús Montes	SJ	Vet. Adm. Hosp. Dallas, Texas	1964 - 1967	1967			
Miguel R. Alonso	SJ	John Hopkins Hosp.	1964 - 1969	1969		1971	Moved to Tampa, FLA.
Robert Ubiñas	SJ	Jefferson Univ. Phila	1969 - 1972	1972			
Renan A. Moretts	Mayaguez	NYEE Inf.	1971 - 1973	1973	1986	1973	Dominican
Raúl Rivera Roldán	Arecibo	Graduate Hosp. Univ. Penn.	1970 - 1974	1974			Died 1994
Kenneth B. Brown	SJ	NYEE Inf.	1946 - 1948	1974		1949	Moved to Naples, FLA.
Gary Montalvo	SJ	Maryland Hosp. Baltimore	1977 - 1980	1980		1981	
Roberto González	Ponce	Brooke Army Hosp. San Antonio, Texas	1978 - 1981	1981		1981	
Lionel Lugo	Ponce	Graduate Hosp. Univ. Penn.	1979 - 1982	1982			
HáctorSantini	Ponce	Univ. So Florida Tampa	1982 - 1985	1985		1985	
Frank Astor	SJ	Cleveland Clinic, Ohio	1980 - 1983	1985		1984	Moved to Florida
Luz Cuebas	Guaynabo	Columbia Univ. NY City	1961 - 1984	1984			
Rafael Caballero	Guayama	SUNY Brooklyn	1980 - 1985	1985			
William SantiagoButler	Ponce	Univ. So Illinois	1980 - 1986	1986			
Julio Ortiz McWilliams	Humacao	Georgetown Univ.	1984 - 1987	1987			
Charles Juarbe	Bayamón	Manhattan EENT	1985 - 1988	1988			



References: **1**. Prescribing Information for Prevnar™, Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein). Lederle Laboratories, Pearl River, NY. **2.** Butler JC, Hofmann J, Cetron MS, et al. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. *J Infect Dis.* 1996;174:986-993.

% only

For Intramuscular Injection Only

See Prescribing Information for complete summary.

INDICATIONS AND USAGE

Prevnar™ is indicated for active immunization of infants and toddlers against invasive disease caused by *Streptococcus pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). The routine schedule is 2, 4, 6, and 12-15 months of age. This vaccine is not intended to be used for treatment of active infection. As with any vaccine, Prevnar™ may not protect 100% of individuals receiving the vaccine. For additional information on usage, see DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication to use of this vaccine. Although a severe or even a moderate febrile illness is sufficient reason to postpone vaccinations, minor illnesses, such as a mild upper respiratory infection with or without low-grade fever, are not generally contraindications.

WARNINGS

THIS VACCINE WILL NOT PROTECT AGAINST *S. PNEUMONIAE* DISEASE OTHER THAN THAT CAUSED BY THE SEVEN SEROTYPES INCLUDED IN THE VACCINE, NOR WILL IT PROTECT AGAINST OTHER MICROORGANISMS THAT CAUSE INVASIVE INFECTIONS SUCH AS BACTEREMIA AND MENINGITIS.

Do not give to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer this vaccine to children with coagulation disorders, it should be given with caution. (See DRUG INTERACTIONS.)

Immunization with Prevnar™ does not substitute for routine diphtheria immunization. Healthcare professionals should prescribe and/or administer this product with caution to patients with a possible history of latex sensitivity since this packaging contains dry natural rubber.

PRECAUTIONS

Prevnar™ is for intramuscular use only and SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY. The safety and immunogenicity of other routes of administration (e.g., subcutaneous) have not been evaluated.

General

CARE IS TO BE TAKEN BY THE HEALTHCARE PROFESSIONAL (HCP) FOR SAFE AND EFFECTIVE USE OF THIS PRODUCT.

1. PRIOR TO ADMINISTRATION OF ANY DOSE OF THIS VACCINE, ASK THE PARENT OR GUARDIAN ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS OF THE VACCINE RECIPIENT. THE HCP SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH THIS VACCINE AND TO ALLOW AN ASSESSMENT OF RISKS AND BENEFITS.
2. BEFORE THE ADMINISTRATION OF ANY BIOLOGICAL, THE HCP SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER ADVERSE REACTIONS. This should include a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.
3. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.
4. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children ≥24 months with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised. Data on sequential vaccination with Prevnar™ followed by 23-valent pneumococcal polysaccharide vaccine are limited. In a randomized study, 23 children ≥2 years of age with sickle cell disease were administered either two doses of Prevnar™ followed by a dose of polysaccharide vaccine or a single dose of polysaccharide vaccine alone; safety and immune responses with the combined schedule were similar to polysaccharide vaccine alone.
5. Since this product is a suspension containing an aluminum adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension prior to withdrawing the dose.
6. Use a separate sterile syringe and needle or a sterile disposable unit for each individual to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.
7. Special care should be taken to prevent injection into or near a blood vessel or nerve.

DRUG INTERACTIONS

As with other intramuscular injections, give Prevnar™ with caution to children on anticoagulant therapy.

During clinical studies, Prevnar™ was administered simultaneously with DTP-HbOC or DTaP and HbOC; OPV or IPV; Hep B vaccines; MMR; and Varicella vaccine. (See Prescribing Information for summary of immune response to routine vaccines when administered with Prevnar™.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Prevnar™ has not been evaluated for any carcinogenic or mutagenic potential, or impairment of fertility.

PREGNANCY

Pregnancy Category C

Animal reproductive studies have not been conducted with this product. It is not known whether Prevnar™ can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. Prevnar™ is not recommended for use in pregnant women.

Nursing Mothers

Prevnar™ is not recommended for use in a nursing mother.

PEDIATRIC USE

Prevnar™ has been shown to be usually well-tolerated and immunogenic in infants. The safety and effectiveness of Prevnar™ in children below the age of 6 weeks have not been established. Immune responses elicited by Prevnar™ among infants born prematurely have not been studied.

GERIATRIC USE

Prevnar™ is NOT recommended for use in adult populations. It is not to be used as a substitute for the pneumococcal polysaccharide vaccine in geriatric populations.

ADVERSE REACTIONS

Overall, the safety of Prevnar™ has been evaluated in a total of five clinical studies in which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age. In addition, the safety of Prevnar™ was evaluated in 560 children from four ancillary studies who started immunization at 7 months to 9 years of age. (See Prescribing Information for summary of local reactions and systemic events reported for the efficacy and all ancillary studies.)

The majority of the safety experience with Prevnar™ comes from the Northern California Kaiser Permanente Efficacy Trial in which 17,066 infants received 55,352 doses of Prevnar™ and 17,080 children received a total of 55,387 doses of the control vaccine (investigational meningococcal group C conjugate vaccine [MnCC]), along with other routine childhood vaccines through April 1998. Local reactions and systemic events occurring within 48 hours of each dose of vaccine were ascertained by scripted telephone interview on a randomly selected subset of approximately 3,000 children in each vaccine group. The rate of relatively rare events requiring medical attention was evaluated across all doses in all study participants using automated databases.

For subjects who received Prevnar™ at 2, 4, 6, and 12-15 months of age, the occurrence of local reactions, such as erythema, induration, tenderness, and any interference with limb movement, were described. Additionally, limited data on local reactions in previously unvaccinated older children were described. (See Prescribing Information for complete summary.)

With vaccines in general, including Prevnar™, it is not uncommon for patients to note within 48 to 72 hours at or around the injection site the following minor reactions: edema; pain or tenderness; redness, inflammation or skin discoloration; mass; or local hypersensitivity reaction. Such local reactions are usually self-limited and require no therapy. As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks.

Systemic events included fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, fussiness, and rash or hives. (See Prescribing Information for complete summary.)

The following events were reported within 3 days of a dose during follow-up from October 1995 through April 1998 of the 17,066 subjects who received at least one dose of Prevnar™ in the efficacy trial. There were 24 hospitalizations (for 29 diagnoses) as follows: bronchiolitis (5); congenital anomaly (4); elective procedure, UTI (3 each); acute gastroenteritis, asthma, pneumonia (2 each); aspiration, breath holding, influenza, inguinal hernia repair, otitis media, febrile seizure, viral syndrome, well child/reassurance (1 each). There were 162 emergency room visits (for 182 diagnoses) as follows: febrile illness (20); acute gastroenteritis (19); trauma, URI (16 each); otitis media (15); well child (13); irritable child, viral syndrome (10 each); rash (8); croup, pneumonia (6 each); poisoning/ingestion (5); asthma, bronchiolitis (4 each); febrile seizure, UTI (3 each); thrush, wheezing, breath holding, choking, conjunctivitis, inguinal hernia repair, pharyngitis (2 each); colic, colitis, congestive heart failure, elective procedure, hives, influenza, ingrown toenail, local swelling, roseola, sepsis (1 each).

One case of a hypotonic-hyporesponsive episode (HHE) was reported in the efficacy study following Prevnar™ and concurrent DTP vaccines in the study period from October 1995 through April 1998. Two additional cases of HHE were reported in four other studies, and these also occurred in children who received Prevnar™ concurrently with DTP vaccine.

In the Kaiser efficacy study, seizures were reported in 8 Prevnar™ recipients and 4 control vaccine recipients within 3 days of immunization. Of the 8 Prevnar™ recipients, 7 received concomitant DTP-containing vaccines and one received DTaP. Of the 4 control vaccine recipients, 3 received concomitant DTP-containing vaccines and one received DTaP. In the other 4 studies combined, in which 1,102 children were immunized with 3,347 doses of Prevnar™ and 408 children were immunized with 1,310 doses of control vaccine (either investigational meningococcal group C conjugate vaccine or concurrent vaccines), there was one seizure event reported within 3 days of immunization. This subject received Prevnar™ concurrent with DTaP vaccine.

Twelve deaths (5 SIDS and 7 with clear alternative cause) occurred among subjects receiving Prevnar™, of which 11 (4 SIDS and 7 clear alternative cause) occurred in the Kaiser efficacy study from October 1995 until April 20, 1999. In comparison, 21 deaths (8 SIDS, 12 clear alternative cause, and one SIDS-like death in an older child) occurred in the control vaccine group during the same time period in the efficacy study.

In a review of all hospitalizations between October 1995 and August 1999 in the efficacy study for the specific diagnoses of aplastic anemia, autoimmune disease, autoimmune hemolytic anemia, diabetes mellitus, neutropenia, and thrombocytopenia, the numbers of such cases were either equal to or less than the expected numbers based on the 1995 Kaiser Vaccine Safety Data Link data set.

DOSAGE AND ADMINISTRATION

Vaccine Schedule

For infants, the immunization series of Prevnar™ consists of three doses of 0.5 mL each, at approximately 2-month intervals, followed by a fourth dose of 0.5 mL at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth dose should be administered at least 2 months after the third dose.

Previously Unvaccinated Older Infants and Children

For previously unvaccinated older infants and children, who are beyond the age of the routine infant schedule, the following schedule applies:

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3*
12-23 months of age	2†
≥ 24 months through 9 years of age	1

*2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.

†2 doses at least 2 months apart.

(See Prescribing Information: CLINICAL PHARMACOLOGY section for the limited available immunogenicity data and ADVERSE EVENTS section for limited safety data corresponding to the previously noted vaccination schedule for older children.)

Safety and immunogenicity data are either limited or not available for children in specific high risk groups for invasive pneumococcal disease (e.g., persons with sickle cell disease, asplenia, HIV-infected).

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Manufactured by:
Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965 U.S.A.
U.S. Govt. License No. 17

Marketed by:
WYETH LEDERLE
VACCINES
Wyeth-Ayerst Laboratories
Philadelphia, PA 19101 U.S.A.

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Artículos Especiales:

Otolaryngology - Head and Neck Surgery Training in Puerto Rico

Dr. Juan Trinidad-Pinedo, F.A.C.S.

Summary

The Otolaryngology-Head and Neck Surgery training program of the University of Puerto Rico, Medical School, is enjoining a full accreditation by the Residency Review Committee of the Accreditation Council for Graduate Medical Education. Since its foundation 76 Otolaryngologist-Head Neck surgeons have graduated, the first class was in 1962 and the last in June 1998, ten of them moved to the mainland where they practice or teach in renown universities.
Our program is five year's durations, and it includes one year of general surgery and four years of progressive education in the specialty. Experience in the surgical sciences will precede the otolaryngology-head and neck surgery education, two residents are accepted each year.

The Puerto Rico program in otolaryngology-head and neck surgery is designed to provide residents with education in the comprehensive medical and surgical care of patients with diseases and disorders that affect the ears, the upper respiratory and upper alimentary systems and related structures, and the head and neck. The educational program includes the core knowledge, skills, and understanding of the basic medical sciences relevant to head and neck; the upper respiratory and upper alimentary systems; the communication sciences, including the knowledge of audiology and speech pathology and audiologic and speech pathology rehabilitation; and the chemical senses and allergy, endocrinology, and neurology as they relate to the head and neck area. The educational program also includes the clinical aspects of diagnosis and the medical and/or surgical therapy for prevention of the following: diseases, neoplasms, deformities, disorders and /or injuries of the ears, the upper respiratory and upper alimentary systems, the face, the jaws, and other head and neck systems; head and neck oncology; and facial plastic and reconstructive surgery.

Our Department offers a unique experience to the otolaryngology resident. The Otolaryngology-Head and Neck Surgery residency program is organized by the School of Medicine of the University of Puerto Rico. It is designed to provide progressive experiences in the management of Otolaryngology Head and Neck Surgery diseases, culminating to independent clinical responsibility during the senior resident year. We strongly support the importance of maintaining a careful balance between independence, and responsibility. We expect that all trainees finish the residency with a broad understanding of OTO-HNS physiology, and diseases with technical expertise in the specialty. The School of Medicine has a consortium with the teaching hospitals the University Hospital, the University Pediatric Hospital, San Juan City Hospital, Oncologic Hospital and Veteran's Administration Hospital and gives residents a strong clinical experience.

Following completion of the educational program, residents will be prepared to care for patients of all ages with medical and surgical disorders of the ears, the uppers respiratory and upper alimentary systems and related structures, and the head neck; to carry out the diagnostic evaluations of patients with otolaryngology disorders; and to carry out the surgical and non surgical management of otolaryngology disorders, including rehabilitation.

Our program is five year's durations, it includes one year of general surgery and four years of progressive education in the specialty. Experience in the surgical sciences will precede the otolaryngology-head and neck surgery education. The final year of the four years of otolaryngology education is a chief resident experience.(1)

Catedrático y Director - Otorrinolaringología-Cirugía de Cabeza y Cuello / Escuela de Medicina - Universidad de Puerto Rico

The Otolaryngology-Head Neck Surgery program of the University of Puerto Rico, Medical School is one of the one hundred participatings in the Otolaryngology Matching Program, candidates have to send their applications through the Central Application Service, the Resident's Selection Committee chooses two candidates each year from applicants.

The program provides surgical and medical education in the following areas:

1. Morphology, physiology, pharmacology, pathology, microbiology, biochemistry, genetics, and immunology relevant to the head and neck; the upper respiratory and upper alimentary systems; the communication sciences, including knowledge of audiology and speech-language pathology; the chemical senses and allergy, endocrinology, and neurology as they relate to the head and neck; and voice sciences as they relate to laryngology.

2. Diagnosis and diagnostic methods: audiologic and vestibular assessments, techniques in voice assessment, electrophisiologic techniques and other related laboratory procedures for diagnosing diseases and disorders of the ears, the upper respiratory and upper alimentary systems, and the head and neck.

3. Therapeutic and diagnostic radiology: the interpretation of medical imaging techniques relevant to head and neck and the thorax, including studies of the temporal bone, skull, nose, paranasal sinuses, salivary and thyroid glands, larynx, neck, lungs, and esophagus.

4. Diagnostic evaluation and management of congenital anomalies, allergy, trauma, and diseases affecting the regions and systems mentioned above.

5. Management of congenital, inflammatory, endocrine, neoplastic, degenerative, and traumatic states, including operative intervention and preoperative and postoperative care of the following major categories:

   a. General otolaryngology
   b. Head and neck surgery
   c. Plastic and reconstructive surgery
   d. Otology
   e. Endoscopy

6. Diagnostic and therapeutic techniques involving the application and utilization of lasers and flexible and rigid perioral endoscopy.

7. The cognitive management, including operative intervention with its preoperative and postoperative care, of congenital, inflammatory, endocrine, neoplastic, degenerative, and traumatic states, including:

   a. Temporal bone surgery
   b. Paranasal sinuses and nasal surgery
   c. Skull-base surgery
   d. Maxillofacial surgery including the orbits, jaws and the facial skeleton
   e. Aesthetic, plastic and reconstructive surgery of the face, head and neck surgery
   f. Surgery of the thyroid, parathyroid, pituitary and salivary glands
   g. Head and neck reconstructive surgery relating to the restoration of form and function in congenital anomalies and head and neck trauma, and associated with ablative operations
   h. Endoscopic, both diagnostic and therapeutic
   i. Surgery of the lymphatic tissues of the head and neck.

8. Habilitation and rehabilitation techniques and procedures including respiration, deglutition, chemoreception, balance, speech, and hearing.

We have a sufficient number and variety of adult and pediatric surgical patients who are available for our resident's education, all residents maintain a cumulative log of their surgical procedures on a computer diskette.

Surgical experience is classified in:

- Salivary Glands
- Nose and Maxilla
- Lips
- Oral Cavity
- Ear
- Neck
- Larynx
- Congenital Anomalies
- Otologic
- Plastic and Reconstructive (otoplasty, rhinoplasty, mentoplasty, rhytidectomy, blepharoplasty, liposuction, chemical and laser peel, dermabrasion, flaps reconstruction, skin grafts, cleft lip and cleft palate repair, scar revision). It has been detailed due to some confused information in the public media.
- Endoscopy
- General

The American Board of Otolaryngology was founded in 1924, and is the second oldest of the twenty-four American certifying boards. The Board defined an otolaryngologist-head and neck surgeon is a physician who has been prepared by accredited

residency programs to provide comprehensive medical and surgical care of patients with diseases and disorders that affect the ears, the respiratory and upper alimentary systems and related structures: the head and neck in general.(2)

Since it is the American Boards philosophy that the specialty should move ahead on a broad front, the examination it conducts has been carefully devised to evaluate the candidate's knowledge in the broad spectrum of head and neck surgery. About 25% of the questions on written and oral examination are devoted to plastic and reconstructive surgery, another 25% to head and neck oncology, about 25% to otology, and the remaining 25% to general otolaryngology.

Between 1992 and 1997, eleven residents completed their training ten passed the Board, this is one index of the quality of specialists graduating in the program..(3,4)

The American Academy of Otolaryngology adopted in 1980 a resolution to call itself the American Academy of Otolaryngology-Head and Neck Surgery. Thus after 28 years of gradual metamorphosis, otolaryngology has acquired an identity that clearly reflects its transformation from an organ specialty into a modern regional specialty encompassing otolaryngology and head and necks surgery.

As knowledge expanded, a therapeutic vacuum developed in the structurally complicated gateway to the body, the head neck area. As a result, the need arose for physicians with special expertise to care for the myriad disorders of this region.

The most logical group to expand and fill the void were the otolaryngologists, by virtue of their unparalleled preparation for the specialty and their control of the clinical material in this area. It soon became evident, however, that the name of the specialty was not descriptive of its member's activities.

Since specialization was first recognized, there has been a trend toward regionalization. Other medical and surgical specialties, such as ophthalmology, neurosurgery, urology, obstetrics, and gynecology have recognized this concept, having become specialists of organ systems or regions. The rest o those in medicine and the public understand the scope of their discipline.(5)

While otolaryngologists have traditionally been designated as the ear, nose, and throat or ENT specialty, these other specialties have no such problem. Ob-gyn specialists, for example, are not called Ovary, Uterus, and Vagina men, nor is the specialty known as OUV. Urologists are not known as Kidney, Ureter, and Bladder men, nor is the specialty known as KUB. Neurosurgeons are not known as Nerve, Brain and Cord men, nor is their specialty known as NBC.

Certainly the letters "ENT" or the words "ear, nose, and throat" do not encompass surgery of the salivary glands, oral cavity, lips, thyroid, major vessels, or peripheral facial nerve; nor do they include facial fracture repair, or pediculed flap procedures from the chest, shoulders, forehead, scalp, and cheek, or mentoplasty, rhytidectomy, blepharoplasty, eyelid repair after tumor removal, base of skull surgery, mandibular surgery, facial implants, scar revision, bronchoscopy, mediastinoscopy and hypophisectomy, to mention a few.

We know that otolaryngoly does not simply mean ear and larynx. Furthermore, it is obvious that the name "ear, nose, and throat" many years ago does not reflect the broad spectrum of problems that the modern otolaryngologist may treat on daily basis.

There is no doubt that the specialty is moving ahead on a broad front. Quality of the individuals entering the profession has increased steadily, as does the quality of the broad training provided within the residency training programs. Some years ago the fifth year of residency training was approved by the Residency Review Committee, the professional qualifications of the practioner in this field has strengthened. The added year has served the worthy purposes of teaching and research, as well as medical practice.

It is abundantly clear that the well-trained otolaryngologist-head and neck surgeon is no longer the ear, nose, and throat physician of the past. He is a complete head and neck physician who has mastered all surgical skills in this area, one who can effectively manage any of the myriad applications in the head neck surgery, whether it is a nosebleed or an extensive cancer operation.

On the other hand, the specialty is clearly constructed of sub specialty building blocks. This emphasis on a particular interest, with associated intensive training, and control of much clinical material, lends itself to super specialization. This trend will produce the higher quality care that people have shown they want.

One problem faced by the otolaryngologist-head and neck surgeon on completing his training, is obtaining hospital privileges. There is universal agreement in the medical profession that the hospital credentialing process is intended to promote the quality of patients care, and protect patients from

incompetent or unqualified physicians. Certain criteria or standards must be met by all who seek clinical staff privilege.

In the area of head and neck surgery, the practice of head and neck plastic surgery is sometimes misunderstood by hospital boards and credentials committees. Judgment is not as easy as might be expected. This is due largely to the fact that involved decision makers tend to think of plastic surgery as a specialty, rather than a method of surgery.

In broad and contemporary context, plastic surgery, may be performed in all areas of the body by the general plastic surgeon, or in areas of specialty practice by a specialty plastic surgeon. The latter may be an otolaryngologist-head and neck surgeon, ophthalmologist, dermatologist or maxillofacial surgeon in the head and neck area—or an orthopedic surgeon, urologist, gynecologist, or other medical specialist concerned with other areas of the body. The practice of regional or organal plastic surgery within the various specialties has simply advanced over years with the trend toward medical specialism.

Overlapping clinical interests of physicians are here to stay. That reality makes imperative the need for puristic discipline in the delineation of hospital staff privileges. Credentials committees should beware of discrimination, which can occur when a staff member of one specialty withhold his support for a well-qualified physician of a competing surgical persuasion who seeks clinical staff privileges. Unpleasant problems, which need no elaboration, can and do arise under such circumstances.

The AMA adopted Substitute Resolution 88 regarding the delineation of clinical privileges. That resolution stated, in part "Resolved, that it is the American Medical Association policy that individual character, training, competence, experience and judgment be the criteria for granting privileges in hospitals; and be it further resolved, that physicians representing several specialties can and should be permitted to perform the same procedures if they meet criteria...."

This AMA resolution raises the issue of the relevance of board certification as one of the important criteria for granting staff privileges, and recognizes the fact that board certification is a device sometimes used to deny or give carte blanche privileges. The resolution clearly recognizes that the granting of clinical privileges cannot and should not depend on any single criterion, such as board certification or the practioners membership in a particular specialty society.

Several overlapping specialty boards certify physicians for surgery in the head, face and neck area. Regardless of which board certifies them, surgeons had the right to be judged on the basis of their personal qualifications, not specialty label.

The American Board of Medical Specialties recognized that there are various methods for delineating clinical privileges. In making the determination of what privileges a practioner will be permitted to exercise in a hospital, medical specialty certification or subcertification should be considered as only one of several valid and important criteria.(6)

The American College of surgeons a policy statement: When an applicant for privileges in one of the surgical disciplines has completed a residency approved by one of the American Specialty Boards, he may properly be granted privileges to perform surgery within the limit of his education, as defined by the appropriate Board. If he requests privileges outside the areas of training specified by his Board, he should be required to provide evidence of his qualifications by authentification of his training for those additional privileges.

Medicare, The United States Department of Health, Education and Welfare has also expressly prohibited use of single criterion, including board certification, in the delineation of clinical privileges. Section 405.1023(e) (4) of the Medicare Regulation states that: Under no circumstances is the accordance of staff membership or professional privileges in the hospital dependent solely upon certification, fellowship or membership in a specialty body or society. All qualified candidates are considered by the credentials committee....

The Joint Commission on the Accreditation of Hospitals stated: No individual shall be automatically entitled to membership on the medical staff...because he is certified by any clinical examen board. This statement of the JCAH carries an even stronger message for hospitals than do the state and federal regulatory provisions. The JCAH not only negates reliance on single criterion in the delineation of clinical privileges, but further states that the granting of clinical privileges should be based upon the individuals current licensure, training, experience, competence, professional ethics and health status. In delineating clinical privileges for surgical procedures involving the face, neck and head, a hospital need not resolve the jurisdictional claims that may be made by overlapping specialty boards: two physicians, each certified by a

different specialty board, may be accorded clinical privileges to perform some or all of the same procedures to the extent justified by the education, training, judgment and experience of each.

Residents completing training find less than favorable situation, managed-care systems apply a competitive corporate profit-oriented mentally to the delivery of medical care, and this means restrictions on referrals, hospitalization, and surgeries. Cost containment dictates decreased patient's access to specialty care, and our practices are suffering from this. Patients would come into the office knowing that they had a specific otolaryngology problem and do not appreciate very well having to be told a referral is necessary. Some private practice otolaryngologists advocate decreasing the number of residents being trained as a solution to these woes. Unfortunately, while decreasing the number of training slots will eventually decrease the number of additional otolaryngologists entering practice each year, it will not change the vicissitudes of managed care.

Some solution has been suggested:
Do nothing, doing nothing may be a reasonable option. It can be suggested that all we can say with certainty is that it now looks as through there is no need to increase the number of otolaryngologits, maintaining ourselves at current workforce levels may be the best way to meet upcoming challenges.

Reduce residency training positions, perhaps empirically making slight decreases in our numbers now will be best allow us to maintain busy and satisfying practices over next years. In the mind of many institutions is the possibility of reducing 10% of actual positions.

There are clearly more frustrations in practicing medicine than there used to be. These frustrations affect both private and academic practice, and there are no easy fixes.

We have a responsibility to our past, current, and future residents to maintain a good caseload, sufficient practice in independent decision-making, and a reasonable chance of satisfying, lifelong employment. There are many unknowns that will affect us and we have no influence or control over these issues. In 10 and 20 years, the average otolaryngologic practice will be quite different than it is now, but we have no way to accurately predict these changes. The best we can do is speculate about possible scenarios and then position ourselves for maximum flexibility.

Conclusion

The Otolaryngology-Head and Neck Surgery training program of the University of Puerto Rico Medical School, is the only program offering this training in the Island. Since the date of the graduation of the first class 76 specialists completed their training, although after that some of them have moved to a mainland, most remained in Puerto Rico, practicing private medicine, few sharing this practice with academic tasks.

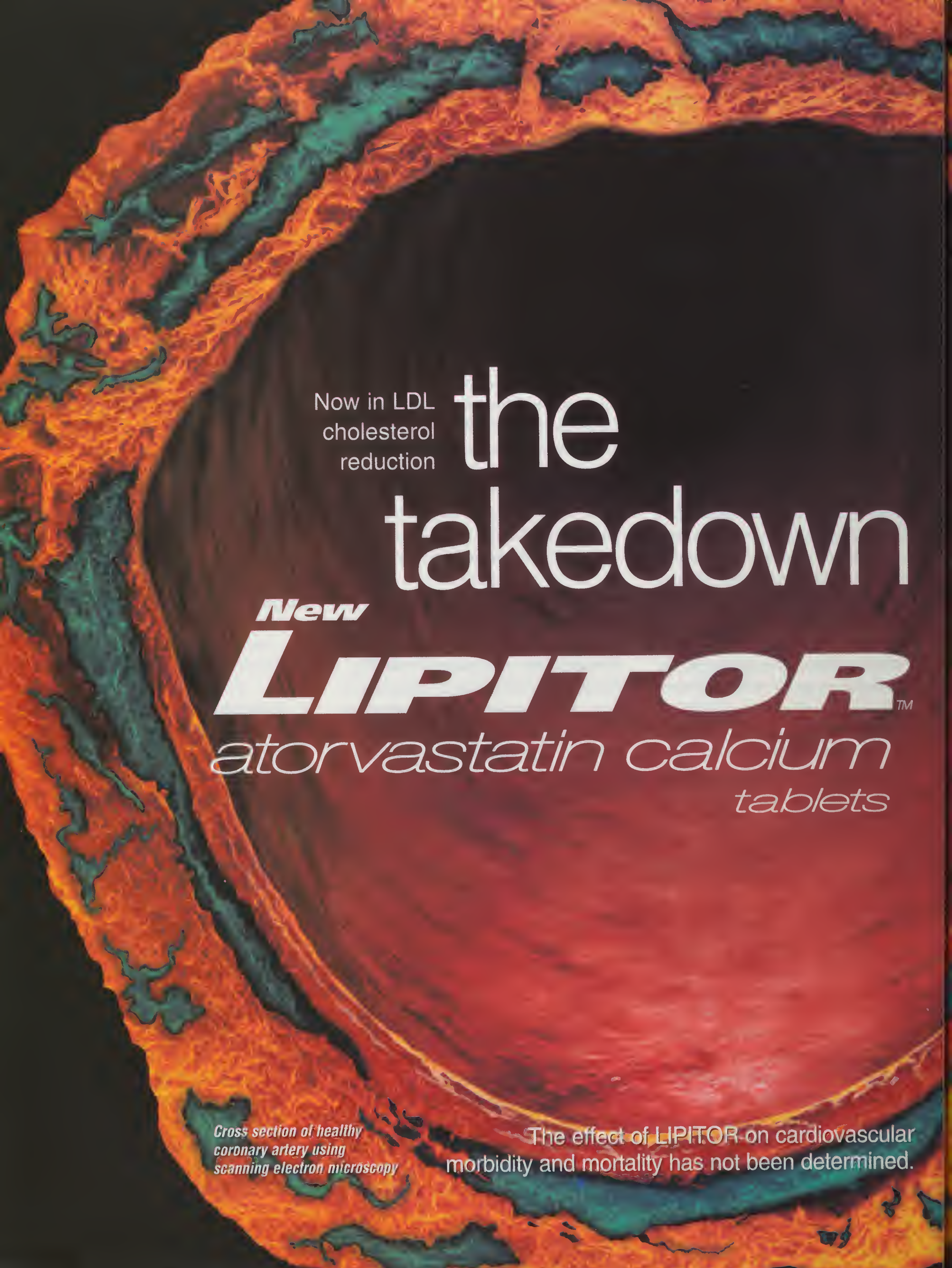
Research has always been an important field in the education of the residents. During the last years, six months of research protected time have been included in the format of the program.

The otolaryngologists reaching private practice face some problems, like getting clinical privileges in the hospitals. Some of the problems encountered are in the area of facial plastic surgery and in dealing with managed-care systems, the former problem has been resolved because the residents interested in this area, after completing training in otolaryngology look for advance education in facial plastic surgery taking the American Board of Facial Plastic Surgery. Certification is a well-accepted evidence of competence by hospital credential committees. At the present, dealing with managed care, continues to be a hassle, including the impact it has had on the number of surgical procedures the resident can perform during his residency.

Reduction in the resident complement (number of residents in a program) is a temporary solution, it will maintain busy satisfying practice over next years and will allow programs to comply with the number of surgical procedures to be performed by each resident as required by the Accreditation Council for Graduate Medical Education.

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Cross section of healthy coronary artery using scanning electron microscopy

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Lipitor™ (Atorvastatin Calcium) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS Active liver disease or unexplained persistent elevations of serum transaminases Hypersensitivity to any component of this medication **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes) Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus

WARNINGS Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively** One patient in clinical trials developed jaundice Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin **It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (eg, semiannually) thereafter** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin Patients who develop increased transaminase levels should be monitored until the abnormalities resolve Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS) **Skeletal Muscle — Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS) Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information) **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever **Drug Interactions** — The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle) ***Antacid:*** When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35% However, LDL-C reduction was not altered ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected ***Colestipol*** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone ***Cimetidine.*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20% Patients taking digoxin should be monitored appropriately ***Erythromycin:*** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle) ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20% These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin ***Warfarin*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment ***Other Concomitant Therapy:*** In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions Interaction studies with specific agents have not been conducted **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS.** Safety in pregnant women has not been established Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2) In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day, pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day, pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH No clinical or biochemical abnormalities were reported in these patients None of these patients was below 9 years of age **Geriatric Use:** Treatment experience in adults age ≥70 years with doses of Lipitor up tc 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Lipitor in this population were similar to those of patients <70 years of age

ADVERSE REACTIONS: Lipitor is generally well-tolerated Adverse reactions have usually been mild and transient In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment, in <2% of patients treated with atorvastatin in clinical trials

Body as a Whole: Face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. ***Digestive System:*** Gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** Pneumonia, dyspnea, asthma, epistaxis ***Nervous System:*** Paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia ***Musculoskeletal System:*** Leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** Urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia. ***Metabolic and Nutritional Disorders:*** Hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance

Caution – Federal law prohibits dispensing without prescription.

Consult package insert before prescribing Lipitor™ (Atorvastatin Calcium) Tablets.

January 1997 0155G021

Pfizer

PD-166-JA-0814-A1(037)
710034

PFIZER Inc.
New York, NY 10017

Reporte de Caso:

What is your Diagnosis?

Ismael Aldrich M.D. FACS

Case Summary

A sixty-five year old male, diabetic, was evaluated at the ENT clinic with a history of a right facial nerve palsy of two years duration. The patient had been treated by his primary physician and had undergone physical therapy. The facial palsy remained unchanged and was awaiting corrective eye surgery because the patient had developed ectropion.

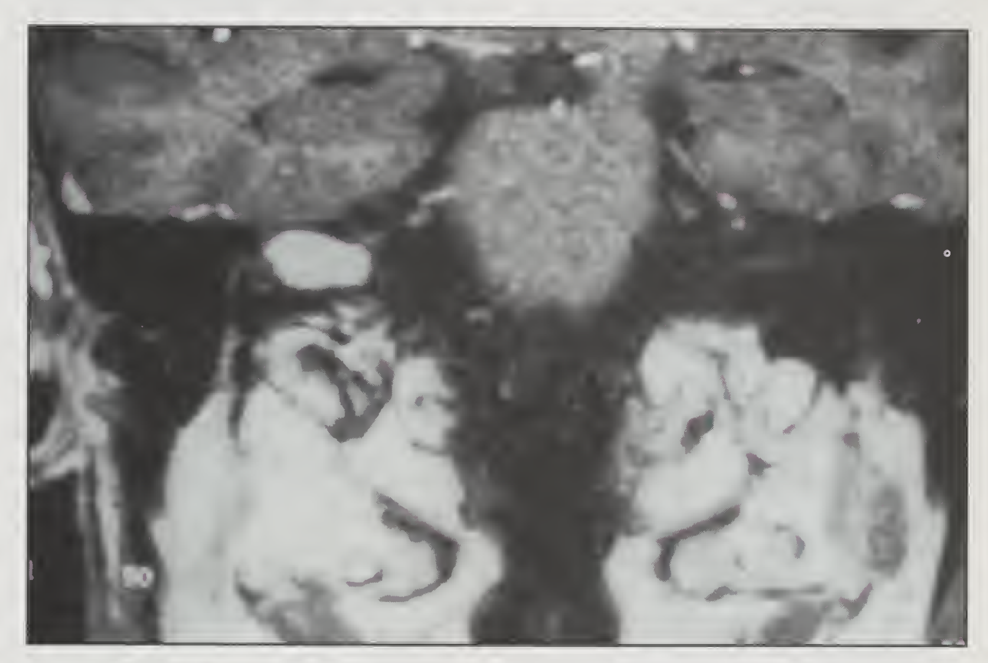
The patient complained that he had developed over the past four months imbalance upon walking and one month prior to the examination developed severe hearing loss in his right ear. His past medical history is significant for Diabetes Mellitus Type II, controled with oral hypoglycemic medication. His fasting blood sugar that morning was 230 mgs.

His physical examination is significant for a long standing facial palsy in the right side with chronic changes like drooping of his right face and ectropion OD. The ear canals and the tympanic membrane were normal. The tunning fork test confirned the severe right ear hearing loss.

A complete audiologic evaluation was obtain which demostrated an right ear profund sensory neural hearing loss. An MRI with contrast was requested. fig. 1. The image demonstrate a mass lesion in the internal auditory canal, which measures 10 by 5 mm in diameter.

What is your diagnosis;

a. Cholesteatoma
b. Acoustic Neuroma
c. Meningioma
d. Squamous Cell Carcinoma
e. All of the above.



Answer: D

Discussion:

In this case the patient had a Squamous Cell Carcinoma of the internal acoustic canal, which could be primary or metastatic. This is a rare case and the pathology was confirmed by the Armed Forces Institute of Pathology A.F.I.P.

Neuromas are the most common tumors found in the internal auditory canal. They are ussually called acoustic neurinomas. They are slow growing tumors, and they are associated with ear symptoms like hearing loss, tinitus, ear fullness, dizzyness and facial palsy. Meningiomas and Cholesteatomas are less frequent. Squamous cell carcinoma of the internal auditory canal is a rare entity and metastatic disease should be suspected.

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Estudios Originales:

Laryngovideostroboscopy

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Juan Trinidad Pinedo, M.D.

This is a convenient and powerful technique that allows the viewing not only of the detailed anatomy of the larynx and related structures but also of the process of phonation (1).

Historical review

The position of the larynx and the difficulty in its illumination have been natural barriers to the development of laryngology. Angled mirrors and candlelight were used initially. Manuel Garcia in 1854 (2) used the sun to visualize his own larynx by reflecting the sunlight with a hand mirror towards the surface of a dental mirror into his larynx. This was the first indirect laryngoscopy. Developments in technique, lighting, and mirror design, first in Europe, then in the United States, further advanced laryngoscopic procedures. An apparatus for suspending the laryngoscope was invented by Killian and this allowed the bimanual instrumentation of the larynx. Electric and distal lighting and monocular and binocular magnifications, introduced in the early 1900s, further advanced laryngeal endoscopy. The combination of direct laryngoscopy, suspension, and the microscope initiated microsuspension laryngoscopy. Also, recently, direct visualization with the flexible and rigid fiberoptic has increased visualization of these areas. Finally, the use of computers and advanced software, videotape recording and high-resolution color monitors and printers has led us to our present state of advancement.

In 1878 Oertel(3) invented the first laryngostroboscope. His instrument was expensive and bulky and, therefore, not useful for otolaryngologists. This tool already had the essence of modern electronic equipment - the stroboscopic pulsating light. This concept was based on a simple perforated disk interpolated between the light source and the examiners head mirror, which was rotated at different speeds. However, the device remained unpopular until the late 20th century when the sophistication of the new technology revived the old stroboscopic concept.

Basic Concepts

Stroboscopy involves the use of intermittent illumination, regulated intervals and multiple exposures of moving vocal folds. It is based on Talbots Law (4) which states that "sequential images produced at intervals shorter than 0.2 seconds persist on the retina and fuse with successive images to produce the optical illusion of apparent motion..." Missing fragments are filled in by the eye, thereby fusing the images and giving the appearance of motion.

This is an old concept that remains valid today and has been propelled into the 21st century by use of the modern technology discussed above, giving rise to the sophisticated technique we call laryngovideostroboscopy.

Stroboscopic Study

Both rigid and flexible scopes can be used in performing stroboscopy. The rigid scope that has a lens angle of 70 degrees or 90 degrees (5) provides magnification and brightness and is used for observation of both structural and vibratory characteristics of the vocal folds. The flexible scope is better for observation of speech and singing (except for vowels). Also the entire supraglottic cavity can be more easily observed using a flexible scope.

The parameters to be included are:

1. The fundamental frequency (Fo)
2. Symmetry
3. Periodicity
4. Amplitude
5. Glottic closure
6. Mucosal waves

Fundamental Frequency

This determination is the first step in the stroboscopy evaluation. Fundamental frequency or "pitch" is an acoustic measure that reflects the vibrating rate of the vocal folds. The unit used is the Hertz (Hz)(6). The measurement is made by monitoring varying speech samples by placing the stethoscope head of

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the laryngeal microphone on the patients neck at the level of the thyroid notch. The patient is given several tasks such as sustained vowel phonation, reading a passage and conversational speech. The fundamental frequency will be determined automatically by the instrument. The stroboscopic light will emit rapid pulses controlled by the extracted fundamental frequency. Should the vocal frequency and the fundamental frequency of the light pulse be the same, the result will appear "static", i.e. the vocal folds will appear "frozen". If the vocal frequency is less or greater than the fundamental frequency the result will give the appearance of the vocal folds in slow motion.

Phase Symmetry

Vocal folds usually vibrate symmetrically and the amplitude or horizontal excursion of the folds is usually the same. Asymmetry is commonly caused by differing mechanical properties of the folds.

Periodicity

Periodicity is defined as the regularity of vocal fold vibration in successive cycles. Aperiodicity or "jitter" is defined as the irregularity of vocal fold vibration in successive cycles. Therefore, stroboscopic flashes synchronized with the frequency of phonation (locked position) will reveal frozen or static image of the vocal folds vibrating periodically.

Amplitude

The extent of horizontal excursion of the vocal folds is referred to as the amplitude. It is rated at normal pitch and normal loudness and during loud and soft episodes.

Glottal Closure

Voice quality is altered when the vocal folds do not close sufficiently during speech. The voice appears "breathy" with decreased intensity. There are several types of incomplete closure and they are so named by the configuration of the folds at closure: complete closure, anterior glottal chink, posterior glottal chink, irregular closure, bowing closure, hourglass closure, and incomplete closure. Additionally important in evaluation is the duration of closure: In hyperfunction – folds close longer, in hypofunction – folds close for a shorter period.

Mucosal Wave

The vocal fold is made up of mucosa and muscle. The mucosa consists of the epithelium and the lamina propia (7). The epithelium is stratified squamous cell epithelium and the lamina propia can be divided into three layers: superficial, intermediate and deep layer.

The superficial layer of the vocal folds is called "Reinke's space" by laryngologists and has histiological and mechanical properties different from those of the body of the vocal folds. The superficial layer vibrates in a wave like motion during speech. The body does not. This mucosal wave is said to be "absent" if it can not be observed. It is deemed "normal" if it is observed to move laterally at approximately half the width of the body of the true fold. It is deemed "small" or "decreased" if the wave motion is contained within the medial edges of the fold.

Other parameters

Further clinical assessment includes arythenoid movement, muscular function, vocal fold edge, vocal fold appearance, peri-arythenoid appearance, and supra/sub glottic tissue appearance.

Analysis

Stroboscope analysis is done visualizing the images on the monitor, either the live image at the time that it is produced or that seen later on in the recording material (FIGURE 1). This is, in fact, a subjective analysis (8). The analysis is improved by seeing a review of the examination using a computerized digital video which permits detailed frame by frame evaluation and further slow motion examination. This will allow even more detailed study with linear

LARYNGOVIDEOSTROBOSCOPY EVALUATION

Fundamental Fo				
Phase Symmetry	Symmetrical	Slight/Mod. Asym.	Severe Asym.	Complete Asym.
Peridicity	Regular	Sometimes Irreg.	Mostly Irreg.	Always Irreg.
Amplitude	Normal	Slight/Mod. Red.	Severe Red.	Complete Red.
Glottic Closure	Complete	Glottal Gap	Mass Obstruc.	Bowing
Mucosal Wave	Normal	Slight/Mod. Red.	Severe Red.	Absent
Arytenoid Mov.	Normal	Slight/Mod. Par.	Severe Par.	Complete Par.
Muscular Function	Normal	Med/Lat. Compr.	A/P Compr.	Mus. Dysfunc.
Vocal Fold Edge	Normal	Irreg. Edges	Mass	Depression
Vocal Fold Appearance	Normal	Edematous	Hyperemic	Inc. Mucous
Peri-arythenoid Appearance	Normal	Edematous	Hyperemic	Pachyderma
Supra&sub-glottic Appearanc.	Normal	Edematous	Hyperemic	Other

and angular measurements for further research in the understanding of laryngeal pathology and physiology. A print with one, two, four (FIGURE 2), eight, and ten color images will reflect the most representative aspects of the stroboscopic evaluation. This is an excellent source of information that can be sent to the referring physician.

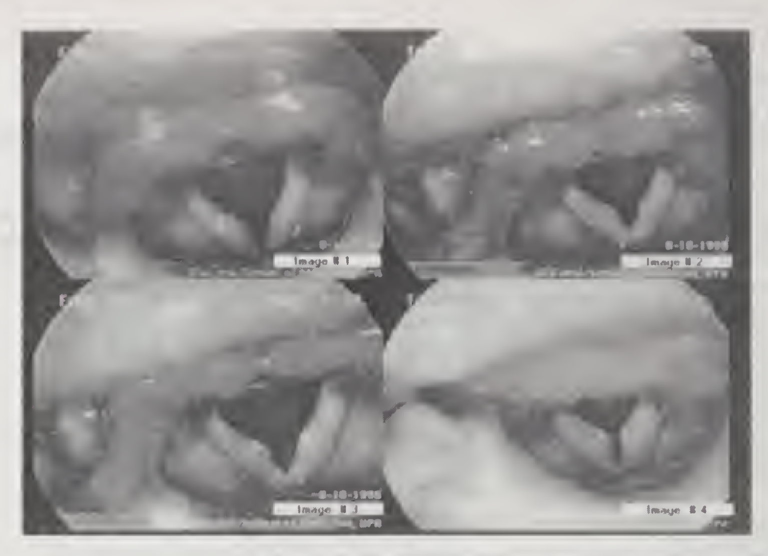


FIGURE 1



FIGURE 2

Results

The University of Puerto Rico, Department of Otolaryngology-Head and Neck Surgery established the "Picó & Rullán Speech and Voice Center". During the first year of its existence the voice disorders identified were as follows:

STROBOSCOPY EVALUATION

Voice Disorders	
Functional (Non-organic)	19 %
Misuse and/or abuse	16 %
Vocal cord nodules	13 %
Vocal cord paralysis	11 %
Spastic dysphonia	11 %
Vocal cord polyps	9 %
Gastroesophageal reflux	7 %
Chronic laryngitis	5 %
Laryngeal web	3 %
Acute laryngitis	2 %
Laryngeal granuloma (nonspecific)	1 %
Ventricular dysphonia (plica ventricularis)	1 %
Reinke's edema	1 %
Supraglottic edema	1 %

Conclusions

Stroboscopy is a technologically advanced technique that is a powerful tool for both practitioners and researchers.

Stroboscopy allows earlier detection of laryngeal disease and improved accuracy in the diagnosis of functional disorders. It also facilitates patient documentation and follow up, before and after surgery and speech rehabilitation and drug therapy.

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Augmentin (amoxicillin/clavulanate potassium) is a registered trademark of SmithKline Beecham Pharmaceuticals.

Zithromax®
(azithromycin for oral suspension)

ONCE DAILY FOR 5 DAYS

ZITHROMAX®
(azithromycin for oral suspension)

BRIEF SUMMARY

INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see **WARNINGS**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Acute otitis media caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

Community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

NOTE: **Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).**

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy. (For specific dosage recommendations, see **DOSAGE AND ADMINISTRATION**.)

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX® may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

ZITHROMAX® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See **CONTRAINDICATIONS**.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function.

There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for Patients: Patients should be cautioned to take ZITHROMAX® suspension at least one hour prior to a meal or at least two hours after a meal. This medication should not be taken with food.

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Drug Interactions: Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Azithromycin did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin–elevated digoxin levels.

Ergotamine or dihydroergotamine–acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolam–decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

Drugs metabolized by the cytochrome P^{450} system–elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use: (**INDICATIONS AND USAGE.**)

Acute Otitis Media (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well controlled studies in adults.

Pharyngitis/Tonsillitis (dosage regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted.

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients (adults and children) from the multiple-dose clinical trials discontinued ZITHROMAX® (azithromycin) therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely.

Clinical: Adults: *Multiple-dose regimen:* Overall, the most common side effects in adult patients receiving a multiple-dose regimen of ZITHROMAX® were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other side effects occurred in patients on the multiple-dose regimen of ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary: Monilia, vaginitis, and nephritis.

Nervous System: Dizziness, headache, vertigo, and somnolence.

General: Fatigue.

Allergic: Rash, photosensitivity, and angioedema.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX® were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX® with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX® were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Children: *Multiple-dose regimens:* The types of side effects in children were comparable to those seen in adults, with different incidence rates for the two dosage regimens recommended in children.

Acute Otitis Media: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%).

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (5.8%), abdominal pain, vomiting, and nausea (1.9% each), and rash (1.6%).

Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%), and headache (1%).

With either treatment regimen, no other side effects occurred in children treated with ZITHROMAX® with a frequency of greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.

Gastrointestinal: Dyspepsia, constipation, anorexia, flatulence, and gastritis.

Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, insomnia.

General: Fever, fatigue, malaise.

Allergic: Rash.

Skin and Appendages: Pruritus, urticaria.

Special Senses: Conjunctivitis.

Post-Marketing Experience: Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria.

Cardiovascular: Arrhythmias including ventricular tachycardia.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration.

General: Asthenia, paresthesia.

Genitourinary: Interstitial nephritis and acute renal failure.

Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice.

Nervous System: Convulsions.

Skin/Appendages: Rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste disturbances.

Laboratory Abnormalities: Adults: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT); with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

Children: Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Acute Otitis Media and Community-Acquired Pneumonia: The recommended dose of ZITHROMAX® for oral suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day).

Pharyngitis/Tonsillitis: The recommended dose for children with pharyngitis/tonsillitis is 12 mg/kg once a day for 5 days (not to exceed 500 mg/day).

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.

ZITHROMAX® for oral suspension should not be taken with food.

More detailed professional information available on request

Revised January 1997

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Pfizer U.S. Pharmaceuticals

Estudios Originales:

Efficacy of Ceftibuten for Pediatric Patients Undergoing Adenotonsillectomy

Charles Juarbe M.D. *

Abstract:

A survey between Otolaryngologist Head and Neck Surgeons in Puerto Rico and a prospective study was done, to evaluate the efficacy of ceftibuten in pediatric patients undergoing adenotonsillectomy.

Surgery of the tonsils and adenoids is the most common operation performed in the pediatric age by the Otolaryngologist Head and Neck Surgeons in Puerto Rico. Over 70% are performed in a ambulatory setting and almost all of the patients are given antibiotics after surgery.

Ceftibuten was given to 112 pediatrics patients after surgery. Adenotonsillectomy is a painfull operation and children do not take medication well after surgery. One of the benefits of this third generation cephalosporin, is that is given once a day. Twenty events were reported taking the medication, but only seven patients had to discontinue its use. Ceftibuten had a tolerance rate of 94%.

Ceftibuten seems to be a safe antibiotic to use in pediatric patients undergoing adenotonsillectomy and has the convenience of being given once a day.

Introduction

Tonsillectomy and Adenoidectomy is one of the most common operations perform in the pediatric age. The Tonsils and Adenoids are located in the oropharynx and nasopharynx. Surgery performed in this anatomic region is considered clean contaminate. Surgical profilaxis with antibiotics is indicated in clean contiminated wounds.(1)

An operation in the oral cavity, like adenotonsillectomy is considered a painful procedure with associated morbidity. Odynophagia, bleeding, fever, halitosis, wound infeccion are some of the complications of surgery. Clinical studies claim that the use of antibiotic in the postoperative period, decreases the morbidity associated with adenotonsillectomy. Beside reducing the incidence of post operative wound infection, it helps promoting wound healing and decrease the incidence of pain, bleeding, fever, mouth odor, and poor oral intake.(2)

Most of these articles were published in the United States in the 1980's. Back then most oral antibiotics had a dose regimine of three or four times a day. No antibiotic has a specific indication as to the surgical profilaxis for adenotonsillectomy. Antibiotics are prescribe empirically, using those that cover bacteria from the upper respiratory tract.

Most textbooks in Otolaryngology Head and Neck Surgery, do not address surgical profilaxis in surgery of the tonsils and adenoid. The author believes this is a standard practice in Otolaryngology Head and Neck Surgery.

Adenotonsillectomy is a painful operation specially in children. Because of the pain kids are reluctant to take medications during the first few days. With the newer antibiotics of single daily dose, it would make sense to use a single daily dose regimen versus a multi daily dose regimen, if it's efficiency would be comparable.

This study was undertaken to see if the use of antibiotics for surgical profilaxis in operations of tonsils and adenoids is prevalent between Otolaryngologist Head and Neck Surgeons in Puerto Rico. The second reason was to evaluate the outcome of the use of Ceftibuten for surgical profilaxis in the pediatric patient undergoing surgery of the tonsils and adenoids.

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Material and Methods

Part A

A questionaire survey was done between the active practitioners of Otolaryngology Head and Neck Surgery in Puerto Rico. There are aproximate 55 active members at the present time. Several questions were ask;

a. Which are the three most common operations you perform?

b. What percent of the pediatric patients that underwent adenotonsillectomy was perform in an ambulatory setting?

c. Do you use antibiotics postoperatively with pediatrics patients undergoing adenotonsillectomy?

d. Mention two of the antibiotics that you prescribe frequently for surgical profilaxis in pediatric patients undergoing adenotonsillectomy?

Part B

An intervention study was done to determine if a single daily dose of antibiotic was effective for surgical profilaxis in pediatric patients having surgery of the tonsils and adenoids. The antibiotic chosen was Ceftibuten. It is a third generation cephalosporin and one of the newer once a day cephalosporin in suspension. A cephalosporin was chosen for this study over other options because in previous studies these were favor by the surgeons.(3)

All the pediatric patients undergoing Adenoidectomy, Tonsillectomy or both, or in conjuction with the placement of presure equalizing tubes were included for the study. The surgery took place at the San Pablo Ambulatory Surgery Unit at San Pablo Hospital and Medical Center between March 1999 and March 2000. The patients with known allergy to penicillin or cephalosporin were excluded. The patient population was operated by the same surgeon. Tonsillectomy was performed using the electrocautery or bovie technic. (4)

Results

Part A

There are fifty-five Otolaryngologist Head and Neck Surgeons in Puerto Rico active in the practice of medicine. Thirty-seven completed the questionaire, including several Pediatric Otolaryngologist Head and Neck Surgeons. This represents over 65% response rate.

The first question ask to mention which were the three most common operation they performed. Two surgeons were excluded from the results because they reported that they did not performed mayor surgery or did not operate. Must mention at this point that two of the surgeons only perform ear surgery.

The most common operation performed was adenotonsillectomy reported by 33 surgeons. The next most common was divided equally between three procedures, ear tympanostomy with the placement of presure equalizing tubes, septoplasty or surgery of the nasal septum and endoscopic sinus surgery. Each procedure reported by 17 surgeons.

The second question ask what percent of the pediatric patients that underwent surgery of the tonsils and adenoids were operated ambulatory. Four surgeons were excluded for the above reasons and three additional were excluded

Table I

Antibiotics used by Otolaryngologist for surgical profilaxis

Type of Antibiotic mention	Num. of Surgeons mentioning the Antibiotic
Amoxicillin	18
Amoxicillin/Clavulanate potasium	2
Azithromycin	2
Cephalosporin as a group	1
Cefechlor	2
Cefprozil	1
Cefpodoxime	1
Cefuroxime	4
Ceftibuten	2
Clarithromycin	1
Clindamycin	2
Cephalexin	2
Erythromycin	2
Loracarbef	6
Penicillin as a group	1

because they did not perform T&A ambulatory only as inpatients hospitalize. Thirty did responde that they do operate tonsils and adenoids ambulatory, but not all of their patients. Multiple percentages were given, but twenty surgeons reported performing surgery of the tonsils and adenoids as an ambulatory procedure in over 70% of the cases.

The next question ask, if they used antibiotic profilaxis in there pediatric patients undergoing adenotonsillectomy. The results were as expected. Thirty-two surgeons used antibiotics post opertive, only one surgeon does not use post operative antibiotics. Four surgeons did not perform this operation. The 32 surgeons who used antibiotics reported a broad selection of products. Thirty-one identified using 13 diferent brand names and two identified using antibiotics as class groups. Table I.

Part B

The parents of 113 patient were given prescription of Ceftibuten after surgery. The dose was calculated for the pediatric patients using the standard dose of 9mg./kg. of weigth, per day. It was given for seven days. Followup included a call at home at 24 hours and were seen at the office at seven days. One patient was excluded from the study group because of allergy to penicillin and cephalosporins not previously identified.

There were 112 pediatric patients who underwent surgery and were given Ceftibuten for seven days. There were 68 males and 44 females. Their age range from 10 months to 18 years of age. The average age was 5.8 years of age. The patient population underwent six different types of operations. 75 adenotonsillectomy, 15 adenotonsillectomy and tube insertion, 13 tonsillectomy, 5 adenoidectomy and tube insertion, 2 adenoidectomy and 2 tonsillectomy with tube insertion. Table II. There were in this group three revision adenoidectomies, two had been performed elsewhere.

The reason for surgery was divided according to the main indications for surgery, between obstructive, infectious or mix. There were 58 cases for obstructive symptoms, 30 cases because infectious and obstructive reasons, and 24 for infectious reasons alone. The patients that had presure equalizing tube inserted, 100% had a complete audiologic evaluation, sustaining the diagnosis of middle ear effusion with various degrees of hearing loss. Eighty-nine patients came to surgery with a positive xray, lateral soft tissue of neck demonstrat-ing enlargment of tonsils and or adenoids or narrowing of the nasopharyngeal airway. A few had abnormal C T scan as well. Patients with severe obstructive sleep apnea and or upper airway resistance syndrome with significant abnormal polysomnogram or sleep study are operated in the hospital as in-patients.

Regarding the general health of the patient population, 40 patients had history of asthma, 5 had history of broncospasm and 3 of croup. Four patients had heart murmurs that antibiotic proplaxis was recommended. Upon routine pathological examination of the surgical specimen, there were 28 cases that the pathologist reported Actinomycosis species colonies in the tonsils. 74 patients got intraoperative steroids, specially the children with history of asthma.

To evaluate the usefullness of Ceftibuten for surgical prophylaxis a strict protocol was followed, any consern, call, question, inquiry by the patients parents was consider an adverse event associated to the use of the antibiotic. There were twenty reported events. Two patients could not buy the antibiotics but was supply by the physician with office samples. There were two patients visits to the Emergency Room, one had severe odynophagia was hydrated and sent home with Tylenol with codeine. The other patient was taken to the ER because had complained of chest pain. He had a full cardiovascular evaluation and it was concluded that it was a muscle spasm. One child who had tubes inserted in his ears, develope otorrhea. Three patients develope diarrhea and another three complained of ear pain, related to the Temporomandibular Joint or TMJ.

Table II

Types of Operations

Procedues Performed	Num. of Cases
Tonsillectomy and Adenoidectomy	75
Tonsillectomy and Adenoidectomy with tubes insertion	15
Tonsillectomy	13
Adenoidectomy with tube insertion	5
Adenoidectomy	2
Tonsillectomy with tube insertion	2

Table III

Adverse Events Reported by the Parents

Event:	Number of cases:	
Diarrhea	3	D*
Ear pain	3	
Could not buy medication	2	
Vomiting	2	D*
Fever	2	
Odynophagia	1	
Chest pain	1	
Rash	1	D*
Spit blood	1	
Halitosis	1	
Allergic reaction	1	D*
Otorrhea	1	
If dose could be divided	1	

D discontinue the use of Ceftibuten*

Two patients develope low grade fever. Vomiting was reported in two patients, which the antibiotic was discontinue. There were two allergic reactions reported by the parents not evaluated by the physician, one develope a rash the other swelling. Both improved with Benadryl and had occured several days after the medication had been started. Must mention each patient was taking several medications. One mother complain of halitosis. Another mother reported his child spit some blood with his saliva. Upon evaluation no bleeding was found and had a blood hemoglobin of 13.6. One parent requested if the dose could be divided because the dose called for two teaspoons. Table III. Of the twenty events reported, 13 did not require to stop taking Ceftibuten, for a tolerance of 94%.

Mayor complications like bleeding, infections, readmission to the hospital or exacerbation of known illness like asthma did not occured.

Discussion

Surgery of the tonsils and adenoids is one of the most frequent operations performed in the pediatric age.(11) Like all surgeries, there can be complications. Some of these are bleeding, pain, infections, halitosis, odynophaged and poor oral intake. Surgery in the oralpharynx is consider a clean contaminated operative field.

Otolaryngologists Head and Neck Surgeons are train under the principles of general surgery, that clean contaminated wounds will require antibiotic prophylaxis.(1) Antimicrobial surgical prophylaxis is indicated in operations of the tonsils and adenoids as recommended by Fairbanks, in Antimicrobial Therapy in Otolaryngology-Head and Neck Surgery(5) and by The American Heart Association(6).

Surgical antimicrobial prophylaxis by definition refers to antibiotics given pre-op and post-op in the first 24 hours after surgery. The efficacy of using antibiotics after 24 hours in preventing wound infections has not been establish. The therapeutic use of antibiotics after surgery has proven to be beneficial reducing the morbidity associated with adenotonsillectomy.

In a controlled study by Teilian et. al., it proves that antibiotic therapy after surgery enhance the recovery of the children undergoing tonsillectomy. Symptoms like fever, pain, halitosis and poor oral intake were minimize.(2) In another report by Grandis et. al. done in adults demostrated that by giving the patients antibiotics after surgery for seven days, this reduce the incidence of fever, pain and halitosis.(7) The antimicrobials used in both studies were given three times a day for seven days.

It is interesting to point out that 74 patients received an intraoperative dose of steroids. Several studies in children by Aprial et. al. and Tom et. al., have demostrated the efficacy of steroids decreasing some of the morbidity associated with adenotonsillectomy (8-9). The favorable outcome of the patients in this study could have been influence by the use of steroids.

The reported adverse events associated with the use of Ceftibuten were very low. The package product insert of Ceftibuten describes under the section of adverse reactions the incidence of these events, diarrhea 4%, vomiting 2% and rash or allergic reaction to less than 1%.(10). In the present study the incidence was less or equal to those reported. This is important because tolerance is as important as efficacy in the pediatric age.

Medicine is continuously changing and evolving. In a prior

report from San Pablo Hospital, demostrated the changing trends regarding surgery of the tonsils and adenoids at that institution which represent the continuous changes in the practice of Otolaryngology-Head and Neck Surgery in Puerto Rico(3). Now there is data covering 18 years regarding the trends of practice with surgery of the tonsils and adenoids in Puerto Rico. In the United States there has been a tendency to perform T&A in an ambulatory setting.(12) In 1983 at San Pablo Hospital over 90% of the adenotonsillectomies were performed as a two day hospital stay admission. In 1993 over 90% of the T&A stayed one day with very few patients done ambulatory. The results from the present report 100% of the patients had their surgery in an ambulatory setting. Data from the survey between the Ear Nose and Throat surgeons in Puerto Rico show that a mayority of the Otolaryngologist Head and Neck Surgeons in Puerto Rico are performing over than 70% of their pediatric adenotonsillectomies as an out patient procedure.

Another comment that can be made from the data is that in 1983 the main indication for surgery was recurrent tonsil infections. Today the main reason is obstructive upper airway symptoms. Back then apnea was not a common word, today we have a full understanding of this sleep disorder in children.

The use of antibiotics postoperativly has been prevalent over the years in the United States and Puerto Rico. This is not a universal practice. In countries like United Kingdom,antibiotics after tonsillectomy are not routinely used. (13). In the the past penicillin was the antimicrobial mostly used, then the cephalosporins. Cephalosporins seems to be favor by many Otolaryngologist in Puerto Rico. Maybe the next logic evolution with the use of antimicrobials should be from a multi daily dose to a single daily dose.

Conclusions

1. Adenotonsillectomy is the most common pediatric operation perform by Otolaryngologist Head and Neck Surgeons in Puerto Rico.
2. The mayority of the Otolaryngologist Head and Neck Surgeons in Puerto Rico operated 70% of there patients having surgery of the tonsils and adenoids in a ambulatory setting.
3. Antibiotics are routinely given after surgery of the tonsils and adenoids in the pediatric age.
4. Ceftibuten seems to be a safe antibiotic to use in pediatric patients having surgery of the tonsils and adenoids. There was a low incidence of adverse reactions and has the convenience of once a day dosing.

Acknowledgments:

To all the Otolaryngologist Head and Neck Surgeons in Puerto Rico that participated filling the survey, thank you.

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Artículos de Revisión:

Actitud Terapéutica en la parálisis Facial

Nelson Fernández Blasini M.D.; F.A.C.S.*

A. Tratamiento de la parálisis facial espontánea idiopática

Medidas terapéuticas especiales

La eficacia del tratamiento de la parálisis facial espontánea idiopática (parálisis de Bell), ha sido un tópico de controversia por décadas, especialmente entre cirujanos y no cirujanos. La literatura publicada en relación a la decompresión médica mediante el uso de corticoesteroides no prueba el que no exista lugar para la decompresión quirúrgica del nervio edematizado.

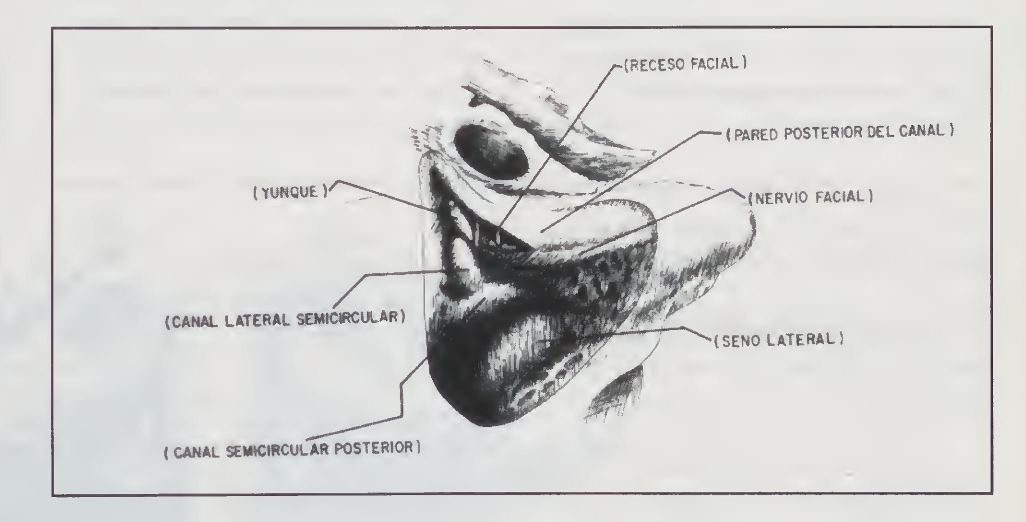
En una gran proporción de casos, estas parálisis recuperan espontáneamente y completamente en un corto periódo de tiempo, con o sin tratamiento, pero aproximadamente en un 15 a 20% de estos casos la recuperación es lenta e incompleta (ej: movimientos sinquinéticos faciales). El tratamiento conservador aparentemente no tiene influencia especlfica en el curso de la enfermedad y sólo los corticoesteroides parecen demostrar mejorla en el curso de la enfermedad si son administrados durante la primera semana luego de el inicio de la parálisis idiopática, asi como la vitamina B12 intramuscular, vasodilatadores y fisioterapia. Es fundamental tener idea del pronóstico de la parálisis, asi como el topodiagnóstico en caso de ser necesaria la decompresión quirúrgica (Dintel de excitabilidad transcutánea mediante estimuladores faciales tipo Hilger). Una diferencia entre los lados de la cara de 3.5 MA indica daño en el nervio. Una disminución lenta en la conductividad del nervio es también indicación de peligro inminente. La prueba del lagrimeo de Schirmer nos determina envolvimiento a nivel del ganglio geniculado.

B. Tratamiento quirúrgico intra-temporal: vias de abordaje. Indicaciones quirúrgicas en la parálisis facial idiopática (Tipo Bell) 1-7

Cuando exista pérdida de función, pero sólo si se encuentran presentes signos de degeneración en electromiografía, dinteles de excitabilidad transcutánea y electrogustometria.

En la parálisis idiopática el tratamiento activo consiste en la decompresión quirúrgica del nervio por via transmastoidea.

La incisión se efectúa, aproximadamente, 1.5 a 2 cm. Posterior al surco retroauricular. Se sigue a través del tejido subcutáneo y periostio desde el borde inferior del músculo temporal hasta la apófisis mastoidea (Figura 1). Se efectúa mastoidectomla transcortical simple bajo irrigación aspiración continua con el contra-angulo de Wülstein o el ototomo de Zimmer y se expone el receso facial. El receso facial, está constituido en su parte superior por



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la fosa del yunque, lateralmente por el nervio de la cuerda del tímpano y medialmente por la porción vertical o descendente del nervio facial.
Se afina el conducto óseo de Falopio usando fresas de diamante bajo irrigación-aspiración contínua para evitar el calentamiento de la fresa. (Figura 2)

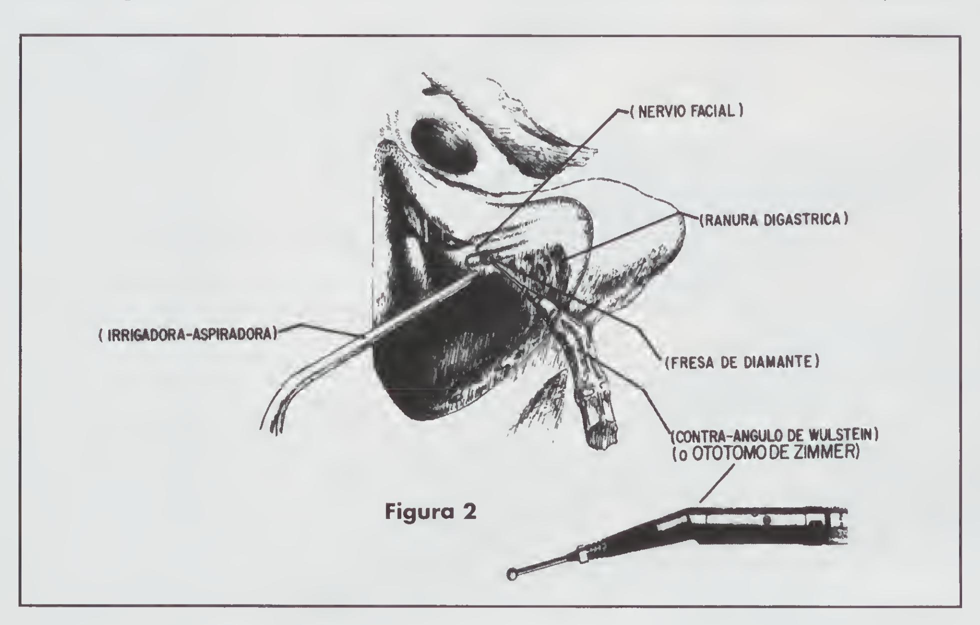


Figura 2

El conducto óseo de Falopio debe ser pulido al máximo antes de extirpar cualquier segmento de él. La cuerda del tímpano se origina de la porción descendente del nervio facial. Se observa el contenido del oído medio a través del receso facial abierto permitiendo el acceso a la porción horizontal del nervio facial a su ganglio geniculado (Figura 3).

Se procede a eliminar la cubierta ósea del canal de Falopio con un gancho dental o espátula (Figura 4).

Se aprecia el segmento vertical del nervio facial sin su cubierta ósea (Figura 5).

Se abre la vaina del nervio facial con un bisturí en hoz, desde el agujero estilomastoideo inferiormente, hasta un punto inmediatamente posterior al ganglio geniculado, de ser necesario (Figura 6).

Cuando se decide a operar, la cirugía debe ser efectuada lo mas pronto posible ya que el nervio puede ser condenado a estrangulación lenta por edema secundario. El edema es causado por espasmo vascular de las arteriolas. Se establece un circulo vicioso en el cual el edema impide la circulación normal y la congestión vascular aumenta la formación del edema. El agente compresor no es solo la pared osea circundante del canal facial (canal de Falopio) en la porción mastoidea o descendente del nervio antes de su salida por el agujero estilomastoideo, sino la vaina fibrosa en dicho segmento vertical la cual en esta región es gruesa y sin fibras elásticas.

Usualmente existe espacio suficiente entre la pared ósea y la vaina fibrosa del nervio. Por lo tanto, si se remueve el canal óseo sin abrir la vaina fibrosa no se efectúa una decompresión efectiva. En otros segmentos en el curso del nervio facial, la vaina es fina y contiene numerosas fibras elásticas.
Por lo tanto, en la mayoría de los casos la decompresión es efectiva en este segmento vertical a menos que el topodiagnóstico revele envolvimiento a nivel del ganglio geniculado en cuyo caso dicha decompresión debe incluir la porción transversa del nervio en el oído medio hasta distal del ganglio geniculado si posible, sin articulación y reposición de la cadena osicular para evitar alguna pérdida auditiva del tipo conductivo (Figura 7).

C. Con envolvimiento LaberÍntico: Decompresión Combinada Transmastoidea-Fosa Media. (House 8, Pulec 2)

Una reducción significante en la prueba del lagrimeo de Schirmer es una indicación para decompresión total del nervio facial utilizando el abordaje transmastoideo previamente descrito, en combinación con el abordaje de fosa media craneal. Se incinden la piel y el músculo temporal

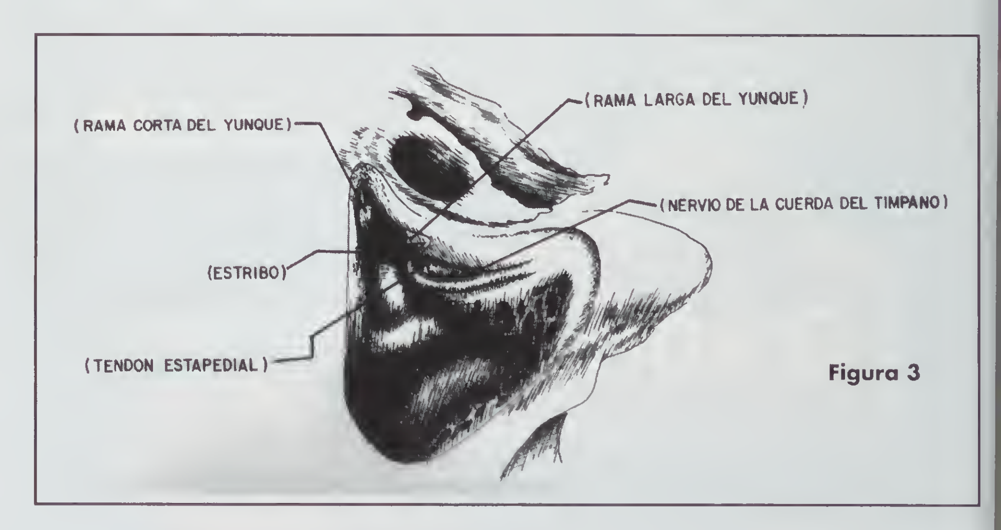


Figura 3

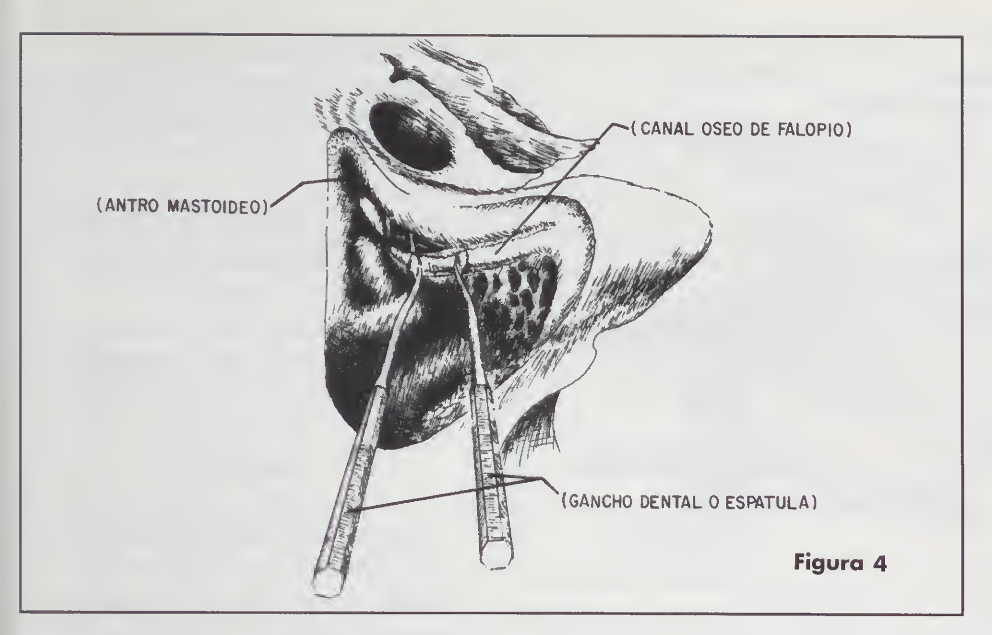


Figura 4

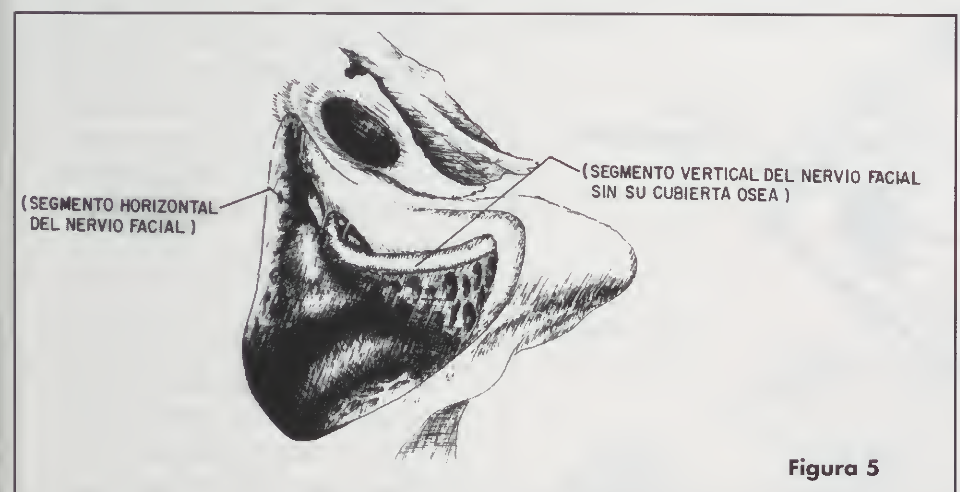


Figura 5

verticalmente y se remueve un cuadrado de hueso temporal utilizando el ototomo de Zimmer bajo el microscopio operatorio y succión-irrigación contínua.
El primer punto de referencia a ser identificado es la arteria meníngea media. Medialmente a ésta se encuentra el nervio petroso superficial mayor que seguido posteriormente nos conduce al ganglio geniculado. Se expone el segmento laberíntico del nervio facial desde el ganglio geniculado medialmente y posteriormente hacia el extremo lateral del canal auditivo interno. Se expone la dura y se identifica la barra ósea de Bill que separa el compartimiento antero-superior del nervio facial, del compartimiento postero-superior del nervio vestibular y se procede a incindir la dura del canal auditivo interno identificando el nervio facial en este compartimiento y procediendo a la decompresión quirúrgica.

Abordaje Retrolaberíntico:

Se efectúa mastoidectomía simple (amplia) y se remueve el hueso sobre el sigmoide y la dura de la fosa posterior. Se incinde la dura paralela y anteriormente al seno sigmoide preservando el saco endolinfático. Se ha abierto el espacio subaracnoideo con flujo de líquido céfalo-raquídeo y según el cerebelo se retrae posteriormente, se exponen los pares craneales quinto, séptimo, noveno y décimo según emergen del tallo cerebral.

Abordaje Translaberíntico:

Se efectúa una mastoidectomía simple y se esqueletoniza el trayecto de nervio facial en su porción vertical o mastoidea hasta su salida por el agujero estilomastoideo.
Se exponen posteriormente los senos petrosos superior y sigmoideo dejando una cubierta osea fina de hueso sobre estas estructuras para su protección. Se efectúa una laberintectomía y se esqueletoniza el canal auditivo interno identificando el canal del nervio vestibular superior y se remueve toda la cubierta osea del nervio facial en su trayecto del canal auditivo interno hasta su salida por el agujero estilomastoideo. (Figura 8)

Reparación del tronco nervioso Intratemporal:

Se define la lesión y se excinden ambos extremos de la misma.

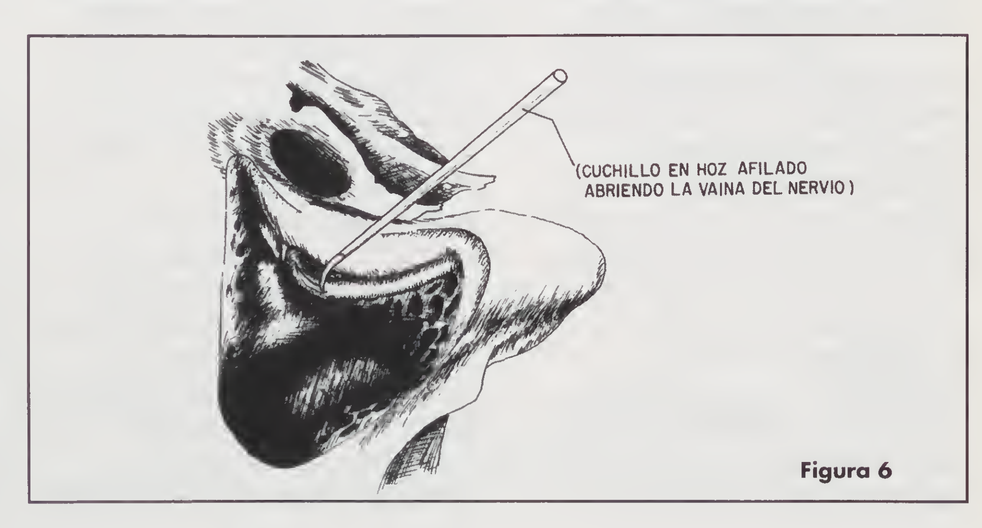


Figura 6

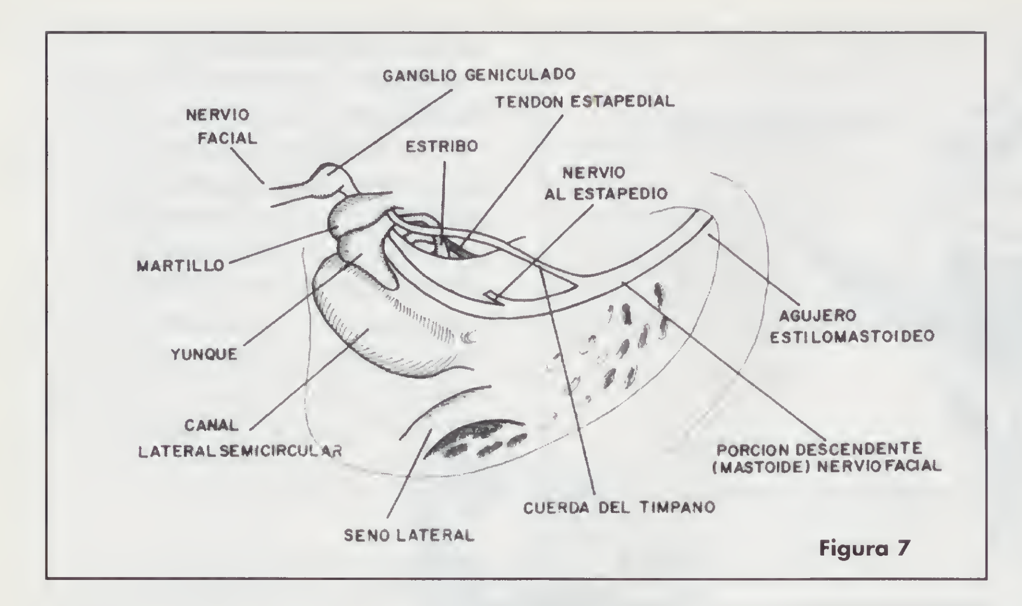


Figura 7

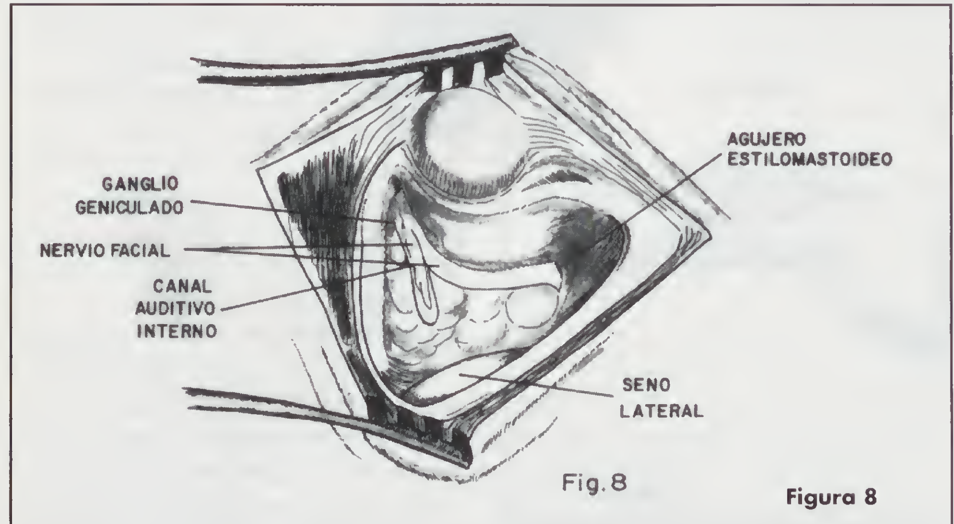


Figura 8

Los segmentos proximales y distales del nervio deben ser seccionados transversalmente en dirección limpia y todo tejido de cicatrización debe ser removido. El espacio no debe ser menos de 1cm. entre ambos muñones o extremos (Figura 9).

El nervio donante puede ser removido del nervio auricular mayor o preferiblemente del nervio cutáneo-lateral del muslo (Figuras 10 y 11). Se debe cortar de 1 a 2mm mayor que el espacio existente en el nervio facial y se coloca en el canal de Falopio. Se ajustan ambos extremos cuidadosamente para aposición efectiva. Para estabilización del injerto se utiliza fibrina fresca, gota a gota en la región reparada.

Tratamiento Quirúrgico Extratemporal:

Ya que la glándula parotida está íntimamente asociada con el trayecto extratemporal del nervio y puede requerir ser removida antes de efectuar cirugía en el nervio facial, se puede efectuar parotidectomía parcial con preservación del nervio facial mediante parotidectomía lateral o parotidectomía total con preservación de dicho nervio.
En caso de existir lesiones que envuelvan la rama principal del nervio o las ramas cervicofaciales o temporofaciales del nervio se encontrará invariablemente alguna forma de deficit permanente.
Así tambien resultan en deficit permanente lesiones proximales a la bifurcación del nervio. Estos defectos pueden ser minimizados con el tratamiento lo más temprano posible.

Injerto del nervio facial lesionado se puede efectuar mediante:
a) Anastomosis directa
b) Anastomosis neural indirecta
c) Transplante de nervio autógeno.

Resúmen

Lesiones que producen parálisis facial pueden ocurrir dentro del hueso temporal en cualquier lugar entre el canal auditivo interno y el agujero estilomastoideo. Exposición quirúrgica de este nervio puede ser necesaria para decompresión en parálisis tipo Bell; injerto, desviación de ruta o remoción de lesiones tal como tumores de colesteatoma, meningiomas o neurinomas del nervio acústico o neuromas del nervio facial.

El objetivo principal en la expocisión quirúrgica del nervio facial en cualquiera de sus segmentos es el de la preservación de la audición y de la función vestibular sin producir mayor lesión a este nervio.

Cuando la audición y la función de balance están presentes la exposición transmastoidea retroarticular nos expone los segmentos timpánicos y mastoideos de dicho nervio. El abordaje de fosa media nos ofrece acceso al canal auditivo interno y la porción laberíntica de dicho nervio facial, mientras que el abordaje retro-laberíntico nos ofrece acceso al nervio en la fosa posterior.
En individuos que han perdido totalmente la función de audicíon y balance, el abordaje retro-auricular translaberíntico ofrece exposición total del nervio facial dentro del hueso temporal y fosa posterior.

En lesiones en la cual el nervio esta afectado en la región parotídea el abordaje es cutáneo lateral en la región cervical superior.

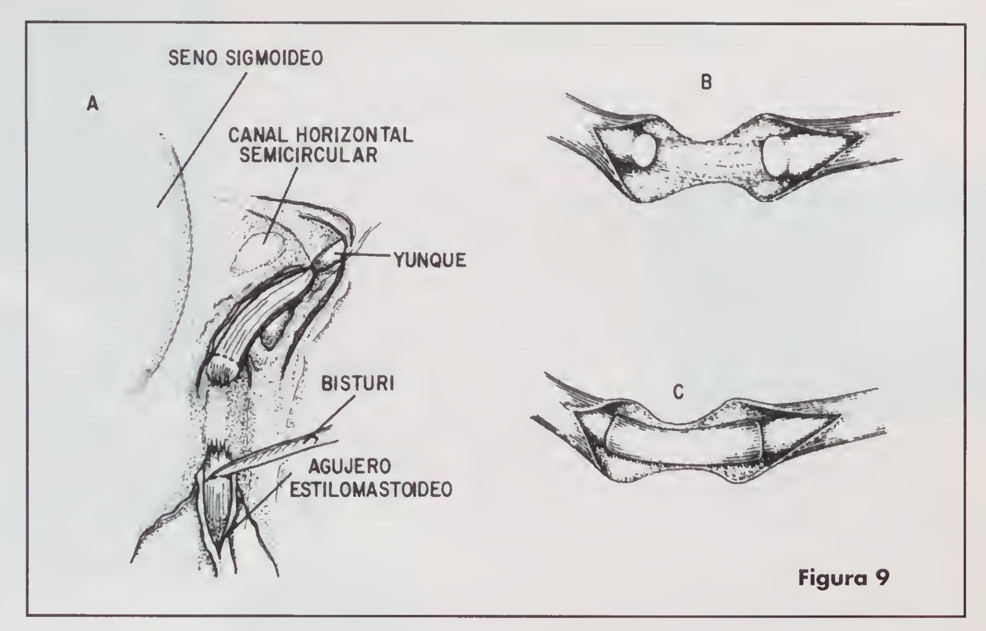


Figura 9

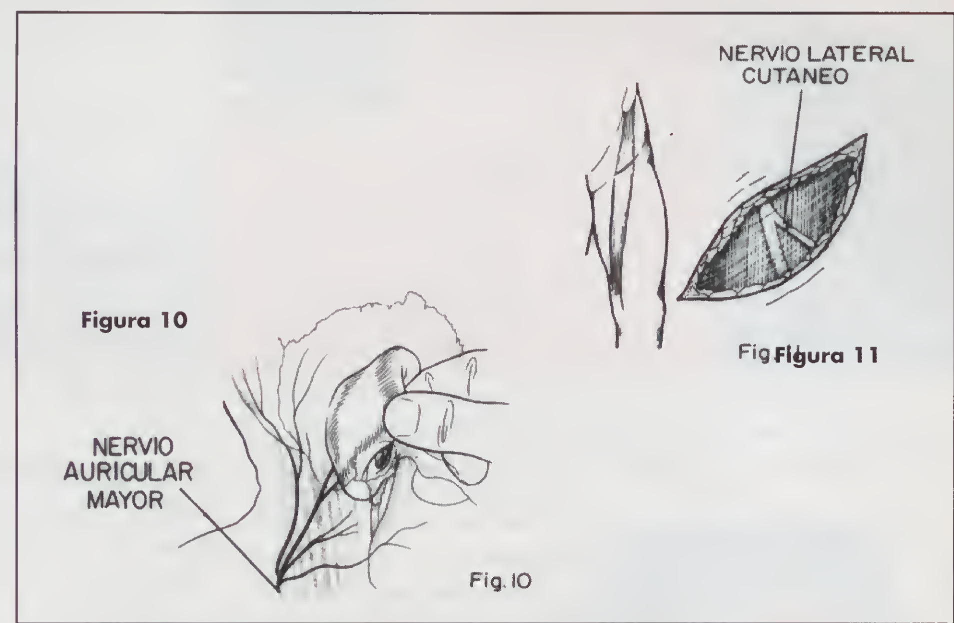


Figura 10

Figura 11

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FLOVENT® 220 mcg
propionato de fluticasona, 220 mcg)
Atomizador para inhalación
Para inhalación oral solamente
A continuación un breve resumen solamente. Véase la información completa sobre prescripción para nformación detallada del producto:
CONTRAINDICACIONES: El atomizador para inhalación FLOVENT está contraindicado en el ratamiento primario de estado asmático u otros episodios agudos de asma donde se requieren nedidas intensivas.
La hipersensibilidad a cualquiera de los ingredientes de estas preparaciones es una contraindicación para su uso.

ADVERTENCIAS:
Se debe tener cuidado particular con los pacientes transferidos de corticosteroides sistémicos activos al atomizador para inhalación FLOVENT ya que han ocurrido muertes a causa de insuficiencia suprarrenal en pacientes asmáticos durante, y después, de la transferencia de corticosteroides sistémicos a otros corticosteroides inhalados menos disponibles sistémicamente. Se requiere cierto número de meses para la recuperación de la función del eje hipotalámico-hipofisario suprarrenal (HPA, por sus siglas en inglés) después de retirar los corticosteroides sistémicos.
Los pacientes a quienes se les mantuvo anteriormente en una dosis de 20 mg o más al dia de prednisona (o su equivalente) podrían ser más susceptibles, particularmente cuando se les ha retirado por completo los corticosteroides sistémicos. Durante este periodo de supresión del HPA, los pacientes pueden mostrar signos y síntomas de insuficiencia suprarrenal al ser expuestos a trauma, cirugia o infección (en particular, gastroenteritis) u otras condiciones asociadas con pérdida severa de electrólitos. Aunque el atomizador para inhalación de propionato de fluticasona puede controlar los síntomas del asma durante estos episodios, en las dosis recomendadas suple sistémicamente menos de las cantidades fisiológicas normales de glucocorticoides y NO provee la actividad mineralocorticoide necesaria para afrontar estas emergencias.
Durante periodos de estrés o un ataque severo de asma, se debe indicar a los pacientes a los que se les han retirado los corticosteroides sistémicos que reanuden los corticosteroides orales (en dosis altas) de inmediato y que se comuniquen con el médico para instrucciones adicionales. También se debe indicar a estos pacientes que lleven una tarjeta de advertencia que indique que pueden necesitar corticosteroides sistémicos suplementarios durante periodos de estrés o de un ataque severo de asma.
Los pacientes que requieren corticosteroides por via oral tienen que disminuir poco a poco el uso de corticosteroides sistémicos después de la transferencia al atomizador para inhalación de propionato de fluticasona. En una prueba con 96 pacientes, se logró reducir con éxito la prednisona reduciendo la dosis diaria en 2.5 mg semanales durante la trasferencia a propionato de fluticasona inhalado. Las reducción sucesiva de la dosis de prednisona se permitió sólo cuando la función pulmonar, los síntomas y el uso de beta-agonistas, según sea necesario, fueron mejores o comparables con lo observado antes del inicio de la reducción de la dosis de prednisona. Hay que vigilar de cerca la función pulmonar (volumen espiratorio forzado1 o tasa de flujo espiratorio máximo AM), el uso de beta-agonistas y los síntomas del asma mientras se retiran los corticosteroides por vía oral. Además de vigilar los signos y síntomas del asma, hay que observar a los pacientes para signos y síntomas de insuficiencia suprarrenal tales como fatiga, cansancio, debilidad, náuseas y vómitos, e hipotensión.
La transferencia de la terapia con corticosteroides sistémicos a un atomizador para inhalación de propionato de fluticasona puede revelar en los pacientes condiciones anteriormente suprimidas por la terapia con corticosteroides sistémicos, p. ej., rinitis, conjunctivitis, eczema y artritis.
Los pacientes que reciben tratamiento con fármacos inmunosupresores son más susceptibles a infecciones que las personas saludables. Por ejemplo, las varicelas y el sarampión pueden tener una evolución más seria o hasta fatal en niños o adultos susceptibles que reciben corticosteroides. Los niños y adultos que no han tenido estas enfermedades, deben ejercer especial cuidado en evitar la exposición. Se desconoce como afecta la dosis, la vía y la duración de la administración de corticosteroides el riesgo de desarrollar una infección diseminada. También se desconoce como pueden contribuir a este riesgo una enfermedad subyacente y/o un tratamiento previo con corticosteroides. Si ha estado expuesto a varicelas, podría estar indicada la profilaxis con la inmunoglubulina de la varicela zoster (VZIG, por sus siglas en inglés). Si ha estado expuesto al sarampión, podría estar indicada la profilaxis con la inmunoglobulina mezclada intramuscular (IG, por sus siglas en inglés). (Véanse las respectivas hojas de información completa sobre prescripción de la VZIG y la IG). Si se desarrollan varicelas, se puede considerar el tratamiento con agentes antivirales.
El atomizador para inhalación de propionato de fluticasona no se puede considerar un broncodilatador y no está indicado para el alivio rápido de broncospasmo. Al igual que con otros medicamentos inhalados contra el asma, puede ocurrir broncospasmo con un aumento inmediato en las sibilancias después de una dosis. Si ocurre broncospasmo luego de una dosis del atomizador para inhalación FLOVENT, hay que tratar de inmediato con un broncodilatador de acción rápida. Se debe descontinuar el tratamiento con el atomizador para inhalación FLOVENT e instituir una terapia alterna.
Se le debe indicar a los pacientes que se comuniquen con su médico de inmediato cuando ocurren episodios de asma que no responden a los broncodilatadores durante el curso de tratamiento con el atomizador para inhalación de propionato de fluticasona. Durante dichos episodios, puede que los pacientes requieran terapia con corticosteroides por vía oral.

PRECAUCIONES:
Generales: Cuando se retiran los corticosteroides por vía oral, algunos pacientes experimentan síntomas de abstinencia de corticosteroides sistémicamente activos, p. ej., dolor en las articulaciones y/o dolor muscular, cansancio y depresión, a pesar del mantenimiento o mejoría de la función respiratoria.
El propionato de fluticasona a menudo permite el control de los síntomas del asma con una supresión menor de la función HPA que las dosis por vía oral terapéuticamente equivalentes de prednisona. Como el propionato de fluticasona se absorbe en la circulación y puede estar sistémicamente activo en dosis mayores, pueden esperarse efectos beneficiosos del atomizador para inhalación de propionato de fluticasona en la minimización de la disfunción HPA solo cuando no se exceden las dosis recomendadas y los pacientes individuales se titulan a la dosis efectiva menor. Se ha demostrado una relación entre los niveles plasmáticos de propionato de fluticasona y los efectos inhibidores en la producción estimulada de cortisol después de 4 semanas de tratamiento con el atomizador para inhalación de propionato de fluticasona.
Puesto que existe sensibilidad individual a los efectos en la producción de cortisol, los médicos deben tomar en consideración esta información al recetar el atomizador para inhalación de propionato de fluticasona.
Debido a la posibilidad de la absorción sistémica de los corticosteroides inhalados, hay que observar cuidadosamente los pacientes tratados con estos fármacos para cualquier evidencia de efectos de los corticosteroides sistémicos. Se debe poner atención especial en observar a los pacientes poscirugía o durante periodos de estrés para evidencia de una respuesta suprarrenal inadecuada.
Es posible que en un número reducido de pacientes surjan efectos de los corticosteroides sistémicos tales como hipercorticismo y supresión suprarrenal, particularmente con dosis mayores. Si ocurren dichos cambios, debe reducirse lentamente la dosis del atomizador para inhalación de propionato de fluticasona en consonancia con los procedimientos aceptados para reducir los corticosteroides sistémicos y para el manejo de los síntomas del asma.
Puede ocurrir una reducción en el ritmo de crecimiento en niños y adolescentes como resultado del control inadecuado de enfermedades crónicas tales como el asma o el uso de corticosteroides para tratamiento. Los médicos deben observar cuidadosamente el crecimiento en los adolescentes que toman corticosteroides, por cualquier vía y si el crecimiento del adolescente parece lento, deben sopesar los beneficios de la terapia con corticosteroides y el control del asma contra la posibilidad de una supresión en el crecimiento.
No se conocen bien los efectos a largo plazo del propionato de fluticasona en sujetos humanos. En particular, se desconocen los efectos resultantes del uso crónico del propionato de fluticasona en los procesos de desarrollo o inmunológicos en la boca, la faringe, la traquea y los pulmones. Algunos pacientes han recibido atomizador para inhalación de propionato de fluticasona continuamente por periodos de 3 años o más. En estudios clínicos con pacientes tratados por casi dos años con propionato de fluticasona inhalado, no se observaron diferencias evidentes en el tipo o severidad de las reacciones adversas después de un tratamiento de largo plazo vis a vis de corto plazo
Se han informado casos raros de glaucoma, aumento en la presión intraocular y cataratas después de la administración inhalada de corticosteroides. En estudios clínicos con propionato de fluticasona inhalado, ha ocurrido desarrollo de infecciones locales de la faringe con Candida albicans. Cuando se desarrollan tales infecciones, se deben tratar con la terapia local o sistémica apropiada (a saber, antifúngica oral) mientras permanece en tratamiento con el atomizador para inhalación de propionato de fluticasona, pero en ocasiones puede que sea necesario interrumpir la terapia con propionato de fluticasona.
FLOVENT® 44 mcg
Los pacientes con infección tuberculosa activa o inactiva del tracto respiratorio, infecciones sistémicas no tratadas por hongos, bacterias, virus o parásitos o herpes simple ocular, deben ejercer cautela con los corticosteroides inhalados, si los usan.
Información para los pacientes: Los pacientes bajo tratamiento con el atomizador para inhalación FLOVENT deben recibir la información y las instrucciones que siguen. El propósito de esta información es ayudar a los pacientes con el uso seguro y efectivo de este medicamento. Esto no constituye una divulgación de todos los efectos adversos o esperados posibles.
Los pacientes deben usar el atomizador para inhalación FLOVENT a intervalos regulares como se indica. Los resultados de las pruebas clínicas indicaron que podría ocurrir una mejoría significativa en el primer día o dos del tratamiento, sin embargo, puede que no se logre el beneficio completo hasta que se haya administrado el tratamiento por 1 a 2 semanas o más. El paciente no debe aumentar la dosis recetada, pero debe comunicarse con el médico si los síntomas no mejoran o si empeora la condición.
Se debe advertir a los pacientes que eviten la exposición a las varicelas o el sarampión y, que de ocurrir una exposición, consulten con su médico de inmediato. Para el uso correcto del atomizador para inhalación FLOVENT y para lograr la mejoría máxima, el paciente debe leer y seguir cuidadosamente las Instrucciones de Uso para el paciente adjuntas.
Carcinogénesis, mutagénesis, deterioro de la fertilidad: El propionato de fluticasona no demostro potencial tumorígeno en estudios de dosis orales de hasta 1,000 mcg/kg (aproximadamente dos veces la dosis máxima de
inhalación humana diaria a base de mcg/m2) por 78 semanas en el ratón o inhalación de hasta 57 mcg/kg (aproximadamente 1/4 de la dosis máxima de inhalación humana diaria a base de mcg/m2) por 104 semanas en la rata.
El propionato de fluticasona no indujo mutación genética en células procarioticas o eucarioticas in vitro. No se detecto efecto clastogeno significativo en el cultivo de linfocitos periféricos humanos in vitro o en pruebas de micronacleos de ratones cuando se administraron a dosis altas por vía oral o subcuanea. Además, el compuesto no retrasó la división eritroblástica en la médula osea.
No se observó evidencia de deterioro de la fertilidad en estudios de reproducción realizados en ratas machos y hembras que recibieron dosis subcutáneas de hasta 50 mcg/kg (aproximadamente 1/4 la dosis máxima de inhalación humana diaria a base de mcg/m2). Sin embargo, hubo una reducción significativa en el peso de la próstata en ratas.
Embarazo: Efectos teratógenos: Embarazo categoría C: Los estudios subcutáneos con ratones y ratas con 45 y 100 mcg/kg, respectivamente (alrededor de 1/10 y 1/2 la dosis máxima de inhalación humana diaria a base de mcg/m2, respectivamente) revelaron características de toxicidad fetal de compuestos glucocorticoides potentes, incluyendo retraso en el crecimiento embrionario, onfalocele, fisura del paladar y osificación craneal retrasada.
En el conejo, se observó reducción en el peso fetal y fisura del paladar después de dosis subcutáneas de 4 mcg/kg (aproximadamente un 25 la dosis máxima de inhalación humana diaria a base de mcg/m2). Sin embargo, después de la administración por vía oral de hasta 300 mcg/kg (aproximadamente 3 veces la dosis máxima de inhalación humana diaria a base de mcg/m2) de propionato de fluticasona al conejo, no hubo efectos en la madre ni aumento en la incidencia de defectos externos fetales, viscerales o esqueléticos. En este estudio no se detectó propionato de fluticasona en el plasma, compatible con la baja biodisponibilidad establecida luego de la administración por vía oral.
(Véase FARMACOLOGIA CLINICA).
Menos del 0.008% de la dosis cruzó la placenta después de la administración por vía oral de 10 0 mcg/kg a ratas ó 300 mcg/kg, 3.6 mg/m2 a conejos (aproximadamente 1/2 y 3 veces la dosis máxima de inhalación humana diaria a base de mcg/m2, respectivamente). No hay estudios adecuados y bien controlados en mujeres embarazadas. El propionato de fluticasona debe usarse durante el embarazo sólo si los beneficios potenciales justifican el riesgo potencial al feto.
La experiencia con glucocorticoides orales desde su introducción en dosis farmacológicas, en oposición a fisiológicas, sugiere que los roedores son más propensos a efectos teratógenos de los glucocorticoides que los humanos. Además, debido a que hay un aumento natural en la producción de glucocorticoides durante el embarazo, la mayoría de las mujeres requieren una dosis menor de glucocorticoides exógenos y puede que muchas no necesiten tratamiento con glucocorticoides durante el embarazo.
No se sabe si el propionato de fluticasona se excreta en la leche humana. La administración subcutánea de fármacos titulados a ratas lactantes (aproximadamente 1/20 la dosis máxima de inhalación humana diaria a base de mcg/m2) resultó en radioactividad medible en el plasma y en la leche. Debido a que otros glucocorticoides se excretan en la leche humana, hay que ejercer cautela cuando se administra el atomizador para inhalación de propionato de fluticasona a mujeres lactantes.
Uso pediátrico: Se trataron ciento treinta y siete (137) pacientes entre las edades de 12 a 16 años con el atomizador para inhalación de propionato de fluticasona en pruebas clínicas fundamentales en EU.

No se ha establecido la seguridad y efectividad del atomizador para inhalación FLOVENT en nios menores de 12 años. Se ha demostrado que el uso extendido los costicosteroides orales causa una reducción en el ritmo de crecimiento de niños y adolescentes.
Si un niño o adolescente que recibe cualquier costicosteroide parece mostrar supresión en el crecimiento, se debe considerar la posibilidad de que sea particularmente sensible a este efecto de los corticosteroides (Véase PRECAUCIONES).
Uso geriátrico: Se han tratado quinientos setenta y cuatro (574) pacientes de 65 os o más con el atomizador para inhalación de propionato de fluticasona en estudios clínicos en y fuera de los EU. No hubo diferencia en las reacciones adversas comparadas con las informadas por pacientes más jóvenes.
REACCIONES ADVERSAS: La siguiente incidencia de experiencias adversas comunes se basa en siete pruebas clínicas controladas con placebo en EU en las que 1,243 pacientes (509 mujeres y 734 varones adolescentes y adultos previamente tratados con broncodilatadores y/o corticosteroides inhalados cuando fuera necesario) fueron tratados con el atomizador para inhalación de propionato de fluticasona (dosis de 88 a 440 mcg dos veces al día hasta por 12 semanas) o placebo
Experiencias adversas generales con incidencia de >3% con el priopionato de fluticasona en pruebas clinicas controladas con Inhalador de Dosis
Medida en pacientes que recibían previamente broncodilatadores y/o corticosteroides inhalados.

Efecto Adverso	Placebo	FLOVENT	FLOVENT	FLOVENT
	(n=475)% dos veces al día (n = 488)%	88 mcg dos veces al día (n = 95)%	220 mcg dos veces al día (n = 185)%	440 mcg
Oido, nariz y garganta				
Faringitis	7	10	14	14
Congestión nasal	8	8	16	16
Sinusitis	4	3	6	5
Secreción nasal	3	5	4	4
Disfonía	1	4	3	8
Rinitis alérgica	4	5	3	3
Candidiasis oral	1	2	3	5
Infección de las vías respiratorias	12	15	22	16
Influenza	2	3	8	5
Dolor de cabeza	14	17	22	17
Duración promedio(en dias)	**44**	**66**	**64**	**59**

La tabla superior incluye todos los eventos*(ya fueran considerados relacionados con el fármaco o no relacionados el fármaco por el investigador) que ocurrieron a una tasa de sobre 3% en los grupos combinados de atomizador para inhalación de propionato de fluticasona y fueron más comunes que en el grupo del placebo. Al considerar estos datos, se deben tomar en consideración las diferencias en la duración promedio a la exposición.

Estas reacciones adversas fueron mayormente de leves a moderadas en severidad y < 1% de los pacientes descontinuaron el estudio debido a los eventos adversos. Se han informado casos raros de reacciones de hipersensibilidad inmediata o retrasada, incluso urticaria y erupción y otros eventos raros de angioedema y broncospasmo.
No se informaron efectos secundarios de los glucocorticoides sistémicos durante las pruebas clínicas controladas con el atomizador para inhalación de propionato de fluticasona. Sin embargo, si se exceden las dosis recomendadas, o si las personas son particularmente sensibles, podrían ocurrir síntomas de hipercorticismo, p. ej., síndrome de Cushing.
Otros eventos adversos que ocurrieron con una incidencia de 1% a 3% en estas pruebas clínicas utilizando el atomizador para inhalación de propionato de fluticasona y que ocurrieron en una incidencia mayor que con el placebo fueron:
Nariz, oído y garganta: Dolor en el/los senos nasales, rinitis.
Ojo: Irritación ocular.
Gastrointestinal: Náuseas y vómitos, diarrea, dispepsia y trastornos estomacales.
Misceláneos: Fiebre.
Boca y dientes: Problemas dentales.
Musculosqueléticos: Dolor en las articulaciones, esguince/torcedura, molestias y dolores, dolor en una extremidad.
Neurológicos: Mareos.
Respitarios: Bronquitis, congestión en el pecho.
Piel: Dermatitis, erupción cutánea.
Urogenitales: Dismenorrea.
En un estudio de 16 semanas de duración con asmáticos que requerían corticosteroides por vía oral, se compararon los efectos del atomizador para inhalción de propionato de fluticasona 660 mcg dos veces al día (n = 32) y 880 mcg dos veces al día (n = 32) con el placebo. Los eventos adversos (ya fueran considerados relacionados con el fármaco o no relacionados con el fármaco por el investigador) informados por más de tres pacientes en el grupo de propionato de fluticasona y que fueron más comunes con el propionato de fluticasona que con el placebo se muestran a continuación: oido, nariz y garganta: Faringitis (9% y 25%); congestión nasal (19% y 22 %); sinusitis (19% y 22%); secreción nasal (16% y 16%); disfonía (19% y 9%); dolor en los senos nasales (13% y 0%; lesiones orales tipo Cándida (16% y 9%); candidiasis orofaríngea (25% y 19%) Respiratorios: Infección en las vías respiratorias superiores (31% y 19%); influenza (0% y 13%). Otros: Dolor de cabeza (28% y 34%); dolor en una articulación (19% y 13%); náuseas y vómitos (22% y 16%); dolor muscular (22% y 13%); malestar general/fatiga (22% y 28%); insomnio (3% y 13%).Observados durante la práctica clínica: Además de los efectos adversos informados en pruebas clínicas, se han identificado los siguientes eventos después del uso postaprobación del propionato de fluticasona en la práctica clínica.

Debido a que se informan voluntariamente de una población de tamaño desconocido, no se pueden hacer estimados de frecuencia. Estos eventos se han escogido para inclusión ya sea por la seriedad, frecuencia de informe, conexión causal al propionato de fluticasona o una combinacin de estos factores.
Oídos, nariz y garganta: Dolor e irritación de garganta, ronquera, laringitis, afonía. Endocrinos y metabólicos: Caracteristicas cushingoides, reducción en la velocidad del crecimiento en nios y adolescentes, aumento de peso, hiperglicemia. Siquiátricos: Intranquilidad, agitación, agresión, depresión.
Respiratorios: Broncospasmo paradójico, exacerbación del asma, disnea, sibilancias, opresión en el pecho, broncospasmo, tos.
Cutáneos: Prurito, contusiones, equimosis. **SOBREDOSIS**: Una sobredosis crónica puede tener como resultado signos/síntomas de hipercorticismo **(véase PRECAUCIONES)**. La inhalación por parte de voluntarios saludables de una sola dosis de 1,760 ó 3,520 mcg del atomizador para inhalación de propionato de fluticasona se tolerá bien. También los voluntarios humanos saludables toleraron bien la administración de atomizador para inhalación de propionato de fluticasona de 1,320 mcg dos veces al día por 7 a 15 días. Se toleraron bien las dosis repetidas de hasta 80 mg diarios por 10 días en voluntarios saludables y dosis repetidas orales de hasta 20 mg diarios por 42 días en pacientes. Las reacciones adversas fueron de severidad de leve a moderada y las incidencias fueron similares en el grupo de tratamiento activo y el del placebo. La dosis letal media oral y subcutánea en ratas y ratones fue de >1,000 mg/kg (>2,000 veces la dosis máxima de inhalación humana diaria a base de mg/m2). DOSIS Y **ADMINISTRACION**: Se debe administrar el atomizador para inhalación de propionato de fluticasona FLOVENT por vía inhalada oral en pacientes de 12 años o más. Los pacientes individuales experimentarán un tiempo variable para el comienzo y el grado de alivio de los síntomas. Por lo general, el atomizador para inhalación de propionato de fluticasona tiene un comienzo de acción relativamente rápido para un glococorticoide inhalado. La mejoría en el control del asma después de la administración inhalada de propionato de fluticasona puede ocurrir no más tarde de 24 horas después de comenzar el tratamiento, aunque puede que no se logre el beneficio máximo hasta 1 ó 2 semanas o más después de comenzar el tratamiento. Una vez se logre la estabilización del asma (véase a continuación), siempre es deseable titular a la dosis efectiva más baja para reducir la posibilidad de efectos secundarios. Para los pacientes que no responden adecuadamente a la dosis inicial después de 2 semanas de terapia, puede que dosis más altas provean control adicional del asma. No se ha establecido la seguridad y eficacia del atomizador para inhalación FLOVENT cuando se administra en dosis más altas que las recomendadas.Se recomienda enjuagarse la boca despues de la inhalación. En la tabla a continuación se indica la dosis inicial recomendada y la dosis más alta recomendada del atomizador para inhalación de propionato de fluticasona, basada en terapias antiasmáticas previas.

Terapia previa	**Dosis inicial recomendada**	**Dosis más alta recomendada**
Broncodilatadores solamente	88 mcg dos veces al día	440 mcg dos veces al día
Corticosteroides inhalados	88-220 mcg dos veces al día*	440 mcg dos veces al dia
Corticosteroides orales H	880 mcg dos veces al día	880 mcg dos veces al día

* Se pueden considerar dosis iniciales sobre los 88 mcg dos veces al día para pacientes con control más deficiente del asma o para los que anteriormente han requerido dosis de corticosteroides inhalados que se encuentran en el límite superior para ese agente específico. **NOTA**: Con todos los pacientes, es deseable titular a la dosis efectiva más baja una vez se haya logrado estabilizar el asma. H Para pacientes que reciben en la actualidad terapia crónica con corticosteroides orales: La prednisona se debe reducir no más rápido de 2.5 mg/día semanalmente, comenzando por lo menos 1 semana después de la terapia con el atomizador para inhalación FLOVENT. Se deben vigilar cuidadosamente los pacientes para signos de inestabilidad asmática, incluyendo medidas objetivas seriadas de flujo de aire y para signos de insuficiencia suprarrenal (**véase ADVERTENCIAS**). Una vez se complete la reducción de prednisona, se debe reducir la dosis de propionato de fluticasona a la dosis efectiva más baja. Uso geriátrico: En estudios donde se han tratado los pacientes geriátricos (**65 años o más, véase PRECAUCIONES)** con el atomizador para inhalación de propionato de fluticasona, la eficacia y la seguridad no se diferenciá de la de pacientes más jóvenes. Por lo tanto, no se recomienda ajustar la dosis. Instrucciones para uso: Instrucciones ilustradas de uso para el paciente que acompañan cada paquete del atomizador para inhalación FLOVENT. PRESENTACION: El atomizador para inhalación FLOVENT 44 mcg viene en cartucho de 7.9-g que contienen 60 inhalaciones medidas en cajas de uno (NDC 0173-0497-00) y en cartuchos de 13-g que contienen 120 inhalaciones medidas en cajas de uno (NDC 0173-0491-00). Cada cartuchos viene con un accionador oral color naranja oscuro con una tapa color melocotón y las instrucciones para los pacientes. Cada activación del inhalador libera 44 mcg de propionato de fluticasona. El atomizador para inhalación FLOVENT 110 mcg viene en cartuchos de 13-g que contienen 120 inhalaciones medidas en cajas de uno (NDC 0173-0494-00). Cada cartucho viene con un accionador oral color naranja oscuro con una tapa color melocotón y las instrucciones para los pacientes. Cada activación del inhalador libera 110 mcg de propionato de fluticasona. Los cartuchos de FLOVENT sólo se utilizarán con los activadores del atomizador para inhalación FLOVENT. No se deben utilizar los accionadores con otros medicamentos en atomizador. Guárdese entre 2E y 30EC (36E y 86EF). Guarde el cartucho con el extremo de la boquilla hacia abajo. Protéjase contra temperaturas de congelación y de la luz directa del sol. Evite rociar en los ojos. Contenido bajo presión. No perfore ni incinere. No guarde a temperaturas sobre los 120EF. Manténgase fuera del alcance de los niños. Para mejores resultados, el cartucho debe estar a temperatura ambiente antes de usarse. Agitese bien antes de usarse. Nota: La ley federal de Aire Limpio requiere sangrar la declaración que aparece a continuación para todos los productos que contienen o se fabrican con clorofluorocarbonos (CFC).**ADVERTENCIA**: Contiene triclorofluorometano y diclorodifluorometano, sustancias nocivas para la salud pública y el ambiente porque destruyen la capa de ozono en la atmósfera superior. Se ha colocado un aviso similar a la **ADVERTENCIA** de arriba en la hoja de información para el paciente de este producto a tenor con los reglamentos de la **Agencia Federal de Protección Ambiental (EPA**, por sus siglas en inglés). El atomizador para inhalación FLOVENT 220 mcg viene en cartuchos de 13-g que contienen 120 inhalaciones medidas en cajas de uno (NDC 0173-0495-00. Cada cartucho viene con un accionador oral color naranja oscuro con una tapa color melocotón y las instrucciones para los pacientes. Cada activación del inhalador libera 220 mcg de propionato de fluticasona.

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Estudios Originales:

Voice Restoration after Total Laryngectomy with Tracheoesophageal Puncture and Voice Prosthesis

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Abstract

Removal of the voice box or larynx is the usual treatment for advanced cancer of the larynx. Tracheoesophageal puncture (TEP) has become an accepted method for voice restoration following total laryngectomy.

Eleven patients under went total laryngectomy with TEP at San Pablo Hospital Medical Center between March 1989 and October 1995. Seven patients were available for voice analysis. Eighty six percent of the patient was able to talk.

This is the first report of TEP being perform in Puerto Rico and with a complete Hispanic population of patients. Results compare favorably with those reported in the medical literature.

Laryngectomy is the usual treatment for advanced laryngeal cancer. The voice is lost as the result of this operation. Tracheo-esophageal puncture (TEP) has become an accepted method for voice restoration following total laryngectomy. Blom and Singer[1], describe the operation for patients with established stomas in 1979 (Secondary TEP). In 1982 Maves and Lingeman[2] describe performing the procedure at the time of laryngectomy (Primary TEP).

Regardless of the timing of the procedure, the goal is to create a fistula between the tracheal stoma and the esophagus. Once the fistula matures the patient is fitted with a voice prosthesis, which permits shunting of air from the trachea into the esophagus, covering the tracheal stoma with the thumb. The patient learns to phonate and develops his new voice.

This study was undertaken to analyze the results of patients undergoing total laryngectomy with TEP and voice prosthesis. To our knowledge this is the first report of results of patients undergoing total laryngectomy and voice restoration with TEP in Puerto Rico.

Methods and Materials:

Between March 1989 and October 1995, 11 patients underwent total laryngectomy with tracheoesophageal puncture at San Pablo Hospital Medical Center. All the patients were operated by the same surgeon.

Of the eleven patients, 10 were male and 1 female. The age range was from 52 to 72 years of age. The mean age was 66 years of age. With regards to the patients past medical history, 3 were hypertensive and one had diabetes mellitus. Nine patients smoked and four gave history of alcohol use. These are important issues because in previews studies preexisting medical problems affected the patient's outcome[3]. All patients had Squamous Cell Carcinoma.
The lesions were located in the following distribution: six glottic, four Supraglottic and one transglottic. Following TMM staging guideline, there was one Stage II, 8 Stage III and 2 Stage IV.

Of the 11 patients who underwent total laryngectomy, five were radiation failure and surgery was required for salvage.
Three patients required preoperative tracheotomy because of airway obstruction.

All the patients had a TEP performed and a cricopharyngeal myotomy. TEP was primary in 10 patients and secondary in one. The surgical technique has been previously describe[2]. Four patients required neck dissection. The TEP

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was stent with a 14 french red rubber catheter and which was also used as a feeding tube. All the patients were fitted with a Bloom Singer voice prosthesis betweens 12th and 17th days post operatively. By week six all the patients were phonating or speaking. All patients had drains place in the wound and antibiotic were given pre and post operatively. No mortality was seen. Complications occurred in two patients. One had a wound infection and the other a fistula that closed with conservative treatment. Follow up ranges from 6 months to 60 months with a mean of 25.5 months. Four patients received post operative radiations therapy. Two of these four patients develop recurrence and were treated with chemotherapy.

Seven patient's remain alive for voice analysis. Two patients died with locoregional disease one, secondary cancer case, and the other was a carotid blow out case.

Complications associated to the use of the voice prosthesis have been few. One patient developal a granuloma at the puncture site which was treated with silver nitrate, and one develop a false pasage that requiened repuncture under local anesthesia.

Results:

There were seven patient's available for voice analysis. A video of the patients was taken having the patients answer specific questions and documenting the patients ability to maintain a conversation between them selfs.

A panel composed of ten nonhealth individuals were used as judges. Prior instructions on voice quality, and voice strenght was given. The physicians, the speech pathologist, and family members were excluded from the evaluation. Then, the video was presented to a group of 10 persons and were ask to evaluate the patients voices.

Voice quality was judged to be excellent in 5 patients, good in one and poor in one. The results for voice strength was reported as 4 excellent, 2 good and one poor. The patient with poor results was a patient who removed the voice prothesis and decided for electrolarynx (Table 1A).

TABLE I(A)
VOICE RESUTS

	EXCELLENT	GOOD	POOR*
VOICE QUALITY	5	1	1
VOICE STRENGHT	4	2	1

* PATIENT REMOVE THE PROSTHESIS

When the patients were asked for degree of satisfaction with their voice, 5 were delighted, one satisfied and one unsatisfied (Table 1B). At present 6 out of 7 (86%) patients continue using the voice prosthesis. Three of the patient's remain active working. The over all result of successful acceptable voice is 86%. Eventhue this is a small group of patients the results were not affected by age, gender, pre-existing medical problem, complications or prior medical treatment. In one report these factor affected the results[3].

TABLE 1(B)
OVERALL PATIENTS SATISFACTION

DELIGHTED	5
SATISFIED	1
UNSATISFIED	1

Discussion:

Since the introduction of TEP with voice prosthesis for vocal rehabilitation after total laryngectomy, the field of vocal rehabilitation has been revolutionized. The literature is full of positive reports of this procedure. TEP has become the main form of vocal rehabilitation after total laryngectomy in the Untied States. The result of multiple series strongly suggests this. (Table II, III, IV).

TEP started as a secondary procedure performed some time after the original surgery. Then TEP was perform at the time of the surgery, primary TEP. At present, it can be perform in extended resection with acceptable results.[4] To our knowledge this is the first report of TEP being perform in Puerto Rico and in a complete hispanic population of patients. The 86% voice result is a number we can now use to express to our prospected patients of the chance of success with the procedure in Puerto Rico. But beyond the numbers it is of great psychological help to the cancer patient to know he will be able to speak at some point after surgical procedure.[22] As demonstrated in this study most patients undergoing total laryngectomy with TEP and placement of voice prosthesis are expected to talk within a short period of time after surgery.

TABLE II
SECONDARY TEP

	YEAR	TOTAL	SUCCESS*
SINGER BLOM, HAMAKER [5]	1981	129	113
WOOD, TUCKER[6]	1981	32	28
WETMORE[7]	1981	18	13
JOHNS, CANTRELL[8]	1981	26	24
DONEGAN, GLUCKMAN, SINGH[9]	1981	23	13
WETMORE, JOHNS, BAKER[10]	1981	61	56
PANJE[11]	1983	120	99
ANDREW, MICKEL, HANSON et. al.[12]	1987	97	NS
PERRY, CHESSMAN, MCIVOR[13]	1987	33	73%
MANIGLIA, LUNDY, CASIANO et. al.[14]	1987	62	43
JUARBE, SHEMEN, WANG et. al.[4]	1989	111	93%

*RESULTS HAVE BEEN REPORTED IN TOTAL SUCCESS NUMBER AND OTHER IN PERCENTAGE. NS NOTG STATED.

TABLE III
PRIMARY TEP

	YEAR	TOTAL	SUCCESS
MAVES, LINGERMAN[15]	1982	11	82%
HAMAKER, SINGER BLOM et.al.[16]	1985	36	75%
SHAGETS, PANGE[17]	1985	60	74%
ANNYAS et. al.[18]	1984	36	86%
JUARBE, SHEMEN, EBERLE et. al.[3]	1985	15	93%
ANDEREW, MICKEL, HANSON et. al.[12]	1987	7	ns
LAU, WEI, HO et al1[9]	1988	33	58%
JUARBE, SHEMEN, WANG et al.[4]	1989	55	97%
MANIGLIA, LUNDY, CASIANO[14]	1989	33	88%

NS NOT STATED

TABLE IV
EXTENDED LARYNGECTOMY WITH FLAP RECONSTRUCTION

	YEAR	TOTAL	SUCCESS
HAMAKER, SINGER BLOM et. al.[16]	1985	6	66%
MEDINA, NANCE, BURN et. al.[20]	1987	10	80%
SALOMON, SWARTZ, JOHNSON et. al.[21]	1987	3	100%
LAU, WEI, HO et. al.[19]	1988	19	83%
JUARBE, SHEMEN, WANG et. al.[4]	1989	10	70%

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Estudios Originales:

Foreign Bodies from the Upper- Aerodigestive Tract of Children in Puerto Rico

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Abstract:

The objective of this study was to investigate the incidence management, and complications of foreign bodies in the upper aerodigestive tract of children in Puerto Rico. The records of children admitted to the University Pediatric Hospital of Puerto Rico were revised from January 1, 1989 to December 31, 1994. 51 children had foreign body in their airway and 107 children had foreign body in their digestive trac (a total of 158 patients) These records were examined for age, gender, previous medical illness, clinical presentation, radiographic studies, removal technique, complications, and hospital stay. The most common age in both groups was 1 year old childrens. Of the 51 foreign bodies aspirations, 25 were boys and 26 were girls; and of the 107 ingestion, 67 were boys and 40 were girls. The most common times of the year were during the summer and winter months. The diagnosis of foreign body aspiration or ingestion was made in 6 hours or less in only 68 of the 158 cases. The most common signs were vomiting, coughing, and choking episode (44 cases). X-rays were positive in 146 cases (92.4%). The most common foreign body ingestion was coins and aspiration was peanuts. There were no complications on 129 cases (81.6%). The most common complication was pneumonia with 19 cases. The mean hospital stay was 3 days. In general, foreign body aspiration or ingestion are common events that can be prevented in the pediatric age. Parental education is important at this stage. If the event can't be prevented then a rapid management must be given to those patients with positive history of an adult witness of the event and a high level of suspicion for those patients with no reported event of choking or witness present.

Introduction:

Foreign body aspiration and ingestion are fairly common problems in the pediatric age. In the United States, over 2000 deaths per year are caused due to choking on food and other foreign bodies, and is the sixth most common cause of accidental death[1]. In 1992, Puerto Rico reported a total of 50 deaths due to aspiration or ingestion of foreign bodies[2]. In 10 of these cases the victims were 14 years old or younger. Young children of one to three years of age are at increased risk of foreipi body aspiration and ingestion. This is explained by the exploration of new textures and tastes due to the orolingual curiosity or tile intention to relieve gum pain due to teething, both being a normal characteristic; of this age. Foreign bodies ingested or aspirated by young children tend to be nuts, coins, hardware, and plastic toy pails, while older children tend to ingest bones,meat, or caustic substances [3]. Symptoms, diagnosis, and treatment depend oil the location and nature of the object.

The purpose of this investigation, devoted to foreign bodies, is to establish number of cases, most common age, sex, object (depending of location), positive or negative x-rays, method or extraction, complications, and average length of hospital stay.

Materials and Methods:

Between January 1, 1989 to December 31, 1994, 158 children were admitted to the University Pediatric Hospital for evaluation and treatment of foreign body aspiration and ingestion. Their medical records were revised for the parameters used to obtain these investigation results. Since there is almost no report of incidence, objects, methods of extraction, or frequency of complication done before this investigation, this will be one of the building stones in the research of this area in Puerto Rico.

The age, sex, previous medical illness, and clinical presentation of patients were evaluated by obtaining the information from the history and physical exam written in the medical records. After careful physical examination, laboratory exams were performed. These included anterior, posterior, and lateral x-ray exams of the neck and chest area. Radiographic evaluation was considered positive if evidence of radiopaque object was evident. In the case of a radiolucent object, the radiographic exam was considered positive if there was

evidence of air trapping of a lung field during expiration, opacity of a lung field, or suggestion of a foreign body in the esophagus during contrast x-rays.

The operation report and progress notes were evaluated for operative procedure, retrieved object, location, complications, and mean hospital stay. Generally, there were four surgical procedures performed in the operating room: direct laryngoscopy, flexible and rigid bronchoscopy, and rigid esophagoscopy. Each of these procedures was used depending on the clinical presentation of each patient. The procedure allowed the proper identification of the foreign object, its location, and removal. Complications include all nonsurgical as well as surgical complications. Nonsurgical complications include all medical illness (or illnesses) attributed to be caused by the foreign object itself, like pneumonia, pulmonary edema, and esophageal tear. Surgical complications include all medical illness (or illnesses) attributed to be caused by removal of the foreign body. These include esophageal perforation, laringospasm, pneumothorax, cardiopulmonary arrest, and others. Mean hospital stay was calculated by using the number of days each patient spent during his or her admission. Since the University Pediatric Hospital is an institution for the medical indigent, it is ilso a great opportunity to evaluate general cost and mean hospital stay.

Results:

Age and sex. 158 patients with airway and esophageal foreign bodies were referred to our institution. Patients age range from 5 months old up to 16 years old. The most common age was 1-year-old children (53 cases). There were all overall total of 92 boys and 66 girls. A total of 51 cases had foreign object aspiration of wich 25 were boys and 26 were girls. From these cases the most common age was 1-year-old with 20 cases reported. Age ranged between 6 months old up to 16 years old. Foreign body ingestion had a total of 107 cases divided in 67 boys and 40 girls. The most common age was also 1-year-old children with a total of 33 cases and the ages ranging from 5 months old to 14 years old.

Month and year. The most common months were January (22 cases), December (17 cases), June (17 cases), July (16 cases), August (16 cases), October (16 cases), and April (13 cases). The distribution of overall cases per year is as follows: 20 cases in 1989, 19 cases in 1990, 34 cases in 1991, 25 cases in 1992, 28 cases in 1993, and 32 cases in 1994. Foreign body aspiration had most of its cases on the months of January (13 cases), December (7 cases), and June (6 cases). The distribution of cases per year was 6 cases in 1989, 10 cases in 1990, 10 cases in 1991, 13 cases in 1992, 7 cases in 1993, and 5 cases in 1994. Foreign body ingestion had a peak of 13 cases in October, 12 cases in July, 11 cases in February, June, and August, 10 cases in April and December, and 9 cases in January. A total of 14 cases were seen in 1989, 9 cases in 1990, 24 cases in 1991, 12 cases in 1992, 21 cases in 1993, and 27 cases in 1994.

Time between aspiration/ingestion and diagnosis. In general, a diagnosis of foreign body aspiration or ingestion was made during the first 6 hours in 68 of 158 cases. Of these, 13 cases (8.22%) were due to foreign body aspiration and 55 cases (34.8%) were due to ingestion. A foreign body was found after one month or more of initial presentation in 4 cases of aspiration and in 3 cases of ingestion. In a total of 39 cases no time span for diagnosis was available. Of these, 7 cases were due to aspiration and 32 cases to ingestion.

Previous illness. The most common overall previous illness was bronchial asthma with 37 cases as the only illness and in 7 cases of patients with multiple previous illnesses. No previous illnesses were encountered in 104 of the 158 patients.

Signs and symptoms. The most common signs and symptoms were vomiting, coughing, and choking (44 cases), dysphagia (39 cases), respiratory distress and drooling (30 cases), cyanosis (14 cases), and fever (11 cases). No symptoms were encountered in 26 cases.

Physical exam. There were no clinical findings in 114 cases (72.2%). The most common clinical findings, including multiple presentations, were wheezing in 23 cases, decreased breath sounds in 19 cases, rhronchus in 13 cases, increased expiratory phase and stridor in 5 cases, and hyperresonance in 1 case. Multiple clinical findings were encountered in 16 cases overall (10.1%). In foreign body aspiration, the most common findings at physical exam of 51 patients were decreased breath sounds and wheezing (19 cases), rhonchus (8 cases), increased expiratory phase (4 cases), and stridor and hyperresonance (1 case each). No clinical findings were present in 17 of the cases (33.3%). In the group of foreign body ingestion, only 14 of 107 patients had a positive clinical examination. The most common findings were rhronchus (5 cases), wheezing and stridor (4 cases), and increased

expiratory phase (1 case). There were 97 cases with a negative physical exam (90.7%).

Radiographic Findings.
In general, x-rays were positive in 146 cases (92.4%). When we segregated the cases in groups, we found that x-rays were positive in 43 out of 51 cases (84.3%) of aspiration and in 103 out of 107 cases (96.3%) of ingestion. Some of the most common radiographic findings in aspiration were hyperlucent lung field in 22 cases, a radiopaque object in 16 cases, pneumonia in 9 cases, and mediastinal deviation in 6 cases. There were 8 negative cases. In foreign body ingestion, we found on x-rays that a radiopaque object was present in 100 cases, contrast esophageal x-rays were positive in 2 cases, atelectasis and pneumonia in 1 case, and negative findings were encountered in 4 cases.

Procedure and duration of foreign body removal. There were a total of 175 procedures performed in 158 patients during these 6 year period. The most common procedures performed were direct laryngoscopy and rigid esophagoscopy with 70 cases (40%). Other common procedures were rigid esophagoscopy with 38 cases (21.7%), direct laryngoscopy and rigid bronchoscopy with 31 cases (l 7.7%), rigid bronchoscopy with 24 cases (l 3.7%), flexible bronchoscopy with 11 cases (6.2%), and one case had suction of the foreign body as treatment (0.5%). The overall mean foreign body removal time was 15.85 minutes, excluding 9 cases with no time specification. Mean time for removal of aspirated body was 27.48 minutes and of ingestion was 9.27 minutes. In 66 of 106 procedures (62.26%) of foreign body ingestion the duration was of 5 minutes or less and in 25 of 60 procedures (41.66%) of aspiration the duration was of 20 minutes or less.

Lodgment site. A total of 151 foreign bodies were recovered, including cases where multiple objects were involved. The most common site of foreign body lodgment was the esophagus at the level of the cricopharyngeal muscle area with 63 objects recovered (39.8%). Other common sites were foreign objects were recovered are the right main bronchus with 21, left main bronchus with 19, upper third of the esophagus with 17, and not specified esophageal location with 13. No object was found after procedure was performed in 7 patients.

Foreign body. The most common foreign bodies identified were coins with 91 cases (57.6%). The most common objects in aspiration of foreign bodies were peanuts (13), sunflower seeds (9), needles (6), beans (2), corn seeds (2), stones (2), and metal screws (2). Ingestion was found to have many common objects, such as coin (91), quenepa seeds (3), jacks (1), and metal springs (1), among others. There were 18 cases of multiple foreign body presentation, 9 aspirations and 9 ingestions. A total of 7 foreign bodies were not found or recovered during procedures, 4 cases in airway and 3 in the gastrointestinal tract. One of them was a rubber balloon spontaneously expelled by a patient with negative flexible bronchoscopies before and after the event.

Complications. In 129 of the cases (81.6%), there was no report of complications. The most common complication was pneumonia with 7 cases (4.4%) as the sole complication and in 12 of 15 cases of patients with multiple complications. Other complications were sepsis (2 cases), broncliospaslil, bronchial edema, esophageal laceration, esophageal tear, and atelectasis (all 1 case). There were a total of 15 cases with multiple complications. Some of the most frequent of these multiple complications were pneumonia (12 cases), mechanical ventilation (8 cases), pulmonary/bronchial edema (8 cases), and cardio-respiratory arrest (4 cases). No deaths were reported.

Hospitalization time. The overall mean hospital stay was 3.04 days. Of these, 83 patients (52.5%) had a hospital stay of 1 day. Foreign body aspiration had a mean hospital stay of 6.20 days. Of the 51 cases of aspiration, 17 patients were in the hospital for 3 days and one patient had a hospital stay of 38 days, which was the longest stay reported. Of the 107 patients of ingestion, the mean hospital stay was 1.54 days, with 81 patients that stayed for one day and the longest stay in this group was one patient with 10 days.

Discussion:

The natural curiosity and experimental nature of children assures that aspiration and ingestion of foreign bodies will require frequent treatment in the emergency rooms of Puerto Rico. Our data shows that 72.15% of the total cases were patients of 3 years old or less (aspiration 74.5% and ingestion 71.02%). This is similar to other studies were the reported incidence of aspiration in children under 3 years of age was 67.5 %[4]. Only 11.3% of the total cases were found to be less than 12 months old. Fven more impressive is that there were only 3 reported cases less than 6 months of age. This may be improbable due to the unskillful hand and inability of these children under 6 months of age to hold objects orally, but the dentition process and

the oral curiosity may drive them to place objects in their mouth. As the maturity starts to come into play, the incidence of children over 12 years of age declines to 6 cases in 6 years. The sex ratio is almost 1.39:1 overall in favor to male patients, but there is a male predominance in ingestion and female in aspiration of foreign bodies.

There are two distinct peaks of cases during the year, from December to January and from June to August. It is interesting to notice that these are precisely the months that children have school vacations. This might explain the incidence of foreign body aspiration / ingestion in children older than 4 years old, but children that had the peak incidence are younger than 3 years of age; so the school factor does not come into play directly on them because they do not attend to school yet. For this reason other factors have to be considered. We have to explore the possibility that these children may be in contact with other older children, as older brothers, cousins, or friends that are free of school duty during these dates and are unintentionally exposing these younger patients to foreign objects. Other factor that has to be investigated is that these months, summer and the holidays, are usually the ones that adults take for vacations too. We have to consider the fact that maybe the adults might be also a key factor in the exposure of small children to foreign objects.

Most of the children will have no history of previous medical illness to worry about when they arrive to the emergency room, but in this study as much as 44 out of 158 cases (27.8%) suffered of bronchial asthma and many require treatment, specially if aspiration is suspected.

It is always preferred to make the diagnosis of a foreign body as soon as possible to benefit the patient and to avoid complications, but not very often the event was witness by an adult. A proper diagnostic time would be the shortest after initiation of symptoms, but sometimes diagnosis could be difficult and delayed. A delayed diagnosis is defined as a diagnosis made after 7 days of the event. Almost half of the cases (48.1%) were diagnosed within the first 15 hours of initiation of symptoms and only 16 cases were diagnosed after 7 days. The longest time to diagnose an object in this study was 4 months. Out of the 158 patients, 68 had a diagnosis of foreign body aspiration or ingestion during the first 6 hours of the event. We can improve this area in two ways: first, having a high level of suspicion with every child that comes in an emergency room with evidence of vomiting, fever, choking, dysphagia, coughing, respiratory distress, drooling, cyanosis, pneumonia, or cold symptoms, a physical exam presenting wheezing, decreased breath sounds, rhonchus, stridor, increased expiratory phase, or hyperresonance, and a highly suspicious x-ray film. Second, having an approximate hour or date of the aspiration or ingestion in order to reach a prognosis based on time of accident, clinical presentation, laboratory results, and radiographic findings.

Radiographic findings are variable depending on the location of the foreign body. Aspiration of a foreign body may produce many x-ray findings, but two presentations are more common: an expiratory check or one-way valve, or an inspiratory check or stop valve. Hyperaeration of a lung field or one-way valve is the most common presentation of the two and in our study it was the most common radiographic finding with a total of 22 out of 51 cases (43.1%). Other authors have described a hyperlucent lung with an incidence from 37.5% up to 50% of cases[4]. The mechanism of one way valve is caused by air that is able to enter the bronchus distal to the foreign body during inspiration, but may not escape from the lung on expiration. This kind of valve obstruction produces emphysema distal to the foreign body. Radiographically, a nondeflating lung field during expiratory films call demonstrate it, but this kind of x-ray is extremely difficult to perform, in a pediatric patient because most of the times they are uncooperative. Another technique to demonstrate easily this finding is by using fluoroscopy of the chest to asses the Hyperaeration of a lung field during expiration and with the use of lateral decubitus chest films of both sides.
The inspiratory check or stop valve completely occludes the bronchus for inspiration and expiration.
This occlusion causes atelectasis of the lung distal to the foreign body because of absorption of the remaining air trapped in the lung. This type of complication is common with aspiration of hygroscopic objects as beans and peas. As these objects are aspirated, they tend to absorb water and obstruct the bronchus completely. In our study, only 3 cases of atelectasis were found. Other important radiological findings of aspiration were radiopaque objects in 16 cases, pneumonia in 9 cases, and niediastinal/ trachea deviation in 6 cases.

Radiopaque foreign objects in the upper gastrointestinal tract call be identified with anterior and lateral views of the neck and chest area. We found that in 100 of 107 cases of foreign body ingestion a radiopaque object was present, the majority being coins. Evidence of a nonopaque object in the esophagus may be suspected by increase distance between the cervical

vertebrae and the larynx and trachea or presence of air in the cervical esophagus. Also a contrast study of the esophagus with a barium sulfate suspension or a water-soluble radiopaque solution may demonstrate the presence of a foreign body. In our study, only 2 cases were positive using contrast studies of the esophagus.

For the 158 patients, a total of 175 procedures were performed during the 6 year period. Of these, 65 procedures were performed in the aspiration group, divided in 29 direct laryngoscopies and rigid bronchoscopies, 24 rigid bronchoscopies, 11 flexible bronchoscopies, 1 direct laryngoscopy and rigid esophagoscopy. There were 110 procedures performed in the ingestion group, divided in 69 direct laryngoscopies and rigid esophagoscopies, 38 rigid esophagoscopies, 2 rigid bronchoscopies, and 1 esophageal section.

The mean procedure time is very important in this study. Not only are we exposing these children to anesthetic agents, but also we are introducing them to the unknown environment of the operating room and are imperative to make this experience as friendly and as short as possible. It is imperative that one of the parents must be present at all times during the emergency room stay, the preoperating room period, and recovery room, whenever possible and not endangering the well-being of the patient or other patients, specially in the pre-operating room and recovery room. This study shows that mean procedure time overall was of 15.85 minutes. The foreign body aspiration mean procedure time was 27.48 minutes, excluding 5 flexible bronchoscopies that had no procedure time reported. As a general rule, the airway endoscopic procedure time should be limited to 30 minutes, because thereafter, the chance of endobronchial and subglottic edema requiring a tracheotomy greatly increases[5]. Sometimes the endoscopic manipulation can pass the 30 minutes time limit to up to 50 to 60 minutes and without the risk of complications or adverse sequelae[5]. The foreign body ingestion mean procedure time was of 9.27 minutes, excluding 4 procedures with no procedure time report, divided in 1 esophageal aspiration performed at the emergency room.

The frequency of lodgment site depends on whether the foreign body was aspirated or ingested. In aspiration, the most common anatomic location of foreign bodies is the right main bronchus or right lower lobe, because the right main bronchus is larger and makes a less of an angle with the frachea than the left bronchus [6-7]. In this study, a total of 47 foreign bodies were recovered and 4 were not recovered in the group of aspiration. The most common location in this study was the right main bronchus with 21 cases and the left main bronchus with 19 cases. This is in accordance to what has been found to be the most frequent location of aspirated objects, but the left main bronchus frequency is very close by. On the other hand, the most common typical location of'esophageal foreign body is immediately below the cricopharyngeal muscle (95% of the cases)[6]. The other locations are the indentation caused by the aortic arch and the left main bronchus, and the area of the lower esophageal sphincter at the gastroesophageal junction. Objects that are smaller than 20 mm will usually be able to pass the normal adult esophagus and a larger object, as coins, button batteries, and meat boluses, will most likely impact themselves[8]. A total of 104 foreign bodies were recovered and 3 were not recovered from the gastrointestinal tract of patients in this study, 2 objects were visualized during procedure at the esophagus, but extraction was not successful and went into the gastrointestinal tract, and in 1 case the object was identified in x-ray films at the esophagus, but it was never found during procedure.

In our study, the most common foreign object in aspiration was peanuts and in ingestion was coins. Similar studies have encountered that peanut are the most common foreign bodies aspirated and coins are the most common ingested[9-10].

The main complications have been linked to a delay in diagnosis time. For example, pneumonia was encountered in 19 cases overall either as sole complication or as pail of multiple complications. There were a total of 17 cases of pneumonia in the aspiration group, of which 14 had a diagnosis time and 3 had no known diagnosis time. Of the 14 cases with known diagnosis time that suffered pneumonia, 3 cases were diagnosed between 2 to 7 hours of the aspiration event (defined as the rapid diagnosis time), 3 cases were diagnosed after 12 to 15 hours, 6 cases were diagnosed after 1 to 14 days of the accidental aspiration, and 2 cases were diagnosed after approximately 1 month. The remaining 2 cases of pneumonia belong to the ingestion group and this happened when diagnosis was delayed in one case for 5 days and in the other for 2 months. Pneumonia was also found to be the most common complication in other studies[4]. If it is true that a rapid diagnosis time will not protect the child from possible complications, this is one of the best weapons we have to prevent more serious complications along the way as

demonstrated by the increased incidence of complications after 7 hours of the event.

In this study, the overall mean hospital stay was of 3.04 days. Foreign body aspiration had amean hospital stay of 6.20 days. This was caused mainly due to an observational period or 48 hours for every patient that undergoes a rigid bronchoscopic procedure and alsodue to the high number of medical complications in this group of patients. The majority of patients stayed form 2 days (21.6%) to 3 days (33.3%), for a total of 28 out of 51 patients (54.9%). Foreign body inigestion had a mean hospital stay of 1.54 days. Out of 107 patients, 81 were discharged home the very same day of admission after proper and full recovery from anesthesia and uucomplicated procedure. The majority of patients were discharged after 1 day (75.7%) to 2 days (17.8%), for a total of 100 out of 107 patients (93.5%).

In summary, foreign body aspiration and ingestion are a fairly common event that can be prevented. It is important to prevent cases by instructing parents, but if the event can't be prevented, we, the physicians, must maintain a high degree of suspicion to be able to diagnose the majority of cases and prevent serious complications. Procedures must be planed in advanced for every patient in order to shorten procedure time and to perform them in a highly effective manner. Complications can be suspected and treated in advanced for the benefit of the patient and to reduce hospital stay. It is our best desire to prevent these cases from happening and to save the live future generations.

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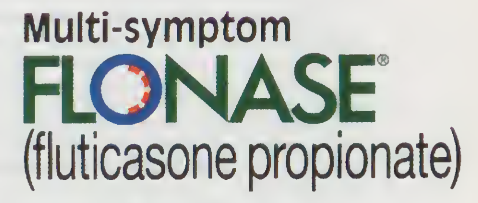
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(propionato de fluticasona)
Spray nasal, 50 mcg

RESUMEN BREVE

AGíTESE SUAVEMENTE ANTES DE USARSE.

Para uso intranasal solamente.

A continuación un breve resumen solamente. Véase la información completa sobre prescripción para información detallada del producto.

INDICACIONES Y USO: El spray nasal FLONASE está indicado para el manejo de síntomas nasales de rinitis alérgica y no alérgica de temporada o permanente en adultos y pacientes pediátricos de 4 años o más.

No se ha establecido adecuadamente la seguridad y eficacia del spray nasal FLONASE en niños menores de 4 años.

CONTRAINDICACIONES: El spray nasal FLONASE está contraindicado en pacientes hipersensibles a cualquiera de sus ingredientes.

ADVERTENCIA: Remplazar un corticosteroide sistémico con un corticosteroide tópico puede ir acompañado de signos de insuficiencia suprarrenal y, además, algunos pacientes podrían experimentar síntomas de abstinencia, p.ej. dolor en las articulaciones y/o los músculos, abatimiento y depresión. Debe mantenerse bajo observación cuidadosa a los pacientes tratados anteriormente con corticosteroides sistémicos por periodos prolongados y cuyo tratamiento se cambió a corticosteroides tópicos, para signos de insuficiencia suprarrenal aguda en respuesta al estrés. El reducir muy rápidamente los corticosteroides sistémicos a pacientes que padecen de asma u otras condiciones clínicas que requieren un tratamiento a largo plazo con corticosteroides, puede ocasionar una exacerbación severa de los síntomas.

El uso concomitante de corticosteroides intranasales con otros corticosteroides inhalados podría aumentar el riesgo de signos o síntomas de hipercorticismo y/o supresión del eje hipotalámico-hipofisario-suprarrenal.

Los pacientes que reciben tratamiento con fármacos inmunosupresores son más susceptibles a infecciones que las personas saludables. Por ejemplo, las varicelas y el sarampión pueden tener una evolución más seria y hasta fatal en pacientes con dosis inmunosupresoras de corticosteroides. Los pacientes que no han tenido estas enfermedades, deben ejercer especial cuidado en evitar la exposición. Se desconoce cómo afecta la dosis, la vía y la duración de la administración de corticosteroides el riesgo de desarrollar una infección diseminada. También se desconoce cómo pueden contribuir a este riesgo una enfermedad subyacente y/o un tratamiento previo con corticosteroides. Si ha estado expuesto a varicelas, podría estar indicada la profilaxis con la inmunoglobulina de la varicela zoster (VZIG, por sus siglas en inglés). Si ha estado expuesto al sarampión, podría estar indicada la profilaxis con la inmunoglobulina intramuscular (IG, por sus siglas en inglés) almacenada [pooled]. (Véanse las respectivas hojas de información completa sobre prescripción de la VZIG y la IG). Si se desarrollan varicelas, se puede considerar el tratamiento con agentes antivirales.

PRECAUCIONES

Generales: En raras ocasiones pueden ocurrir reacciones inmediatas de hipersensibilidad o de dermatitis de contacto después de la administración intranasal del spray nasal FLONASE. Se han informado casos raros de sibilancias, perforación del tabique nasal, cataratas, glaucoma y aumento en la presión intraocular después de una aplicación intranasal de corticosteroides, incluyendo el propionato de fluticasona.

El uso excesivo de dosis de corticosteroides puede conducir a signos o síntomas de hipercorticismo, supresión de la función del eje hipotalámico-hipofisario-suprarrenal y/o supresión del crecimiento en niños y adolescentes. Los médicos deben observar cuidadosamente el crecimiento de los adolescentes que toman corticosteroides, por cualquier vía y si el crecimiento del adolescente parece lento, debe sopesar los beneficios de la terapia con corticosteroides contra la posibilidad de supresión en el crecimiento.

Aunque los efectos sistémicos con dosis recomendadas del spray nasal FLONASE han sido mínimos, el riesgo potencial aumenta con dosis mayores. Por lo tanto, se deben evitar las dosis más altas de lo recomendado del spray nasal FLONASE.

Cuando se utiliza en dosis mayores que las recomendadas, o en casos raros con la dosis recomendada, pueden surgir efectos sistémicos de los corticosteroides tales como hipercorticismo y supresión suprarrenal. Si ocurren dichos cambios, es necesario descontinuar la dosis del spray nasal FLONASE lentamente en consonancia con los procedimientos aceptados para descontinuar la terapia de corticosteroides orales.

En estudios clínicos con propionato de fluticasona administrados intranasalmente, el desarrollo de infecciones localizadas de la nariz y la faringe con Candida albicans ha ocurrido sólo en raras ocasiones. Cuando se desarrolla este tipo de infección, puede que se requiera tratamiento con la terapia local apropiada y la descontinuación del tratamiento con el spray nasal FLONASE. Los pacientes que han estado usando el spray nasal FLONASE por varios meses o más, deben someterse a exámenes periódicos para evidencia de infección con Candida u otras señales de efectos adversos en la mucosa nasal.

Los pacientes con infecciones tuberculosas activas o inactivas; infecciones no tratadas localizadas o sistémicas con hongos o bacterias o virus sistémicos; o infecciones parasíticas; o herpes simple ocular deben ejercer cautela con el uso del spray nasal FLONASE o no usarlo.

Debido al efecto inhibidor de los corticosteroides en la sanación de heridas, los pacientes que han tenido úlceras recientes del tabique nasal, cirugía nasal o trauma nasal, no deben usar un corticosteroide nasal hasta que la herida haya sanado.

Información para los pacientes: Los pacientes bajo tratamiento con el spray nasal FLONASE deben recibir la siguiente información e instrucciones. El propósito de esta información es ayudar a los pacientes con el uso seguro y efectivo de este medicamento. Esto no constituye una divulgación de todos los efectos adversos o esperados posibles.

Se debe advertir a los pacientes que eviten la exposición a las varicelas o el sarampión y, que de ocurrir una exposición, consulten con su médico de inmediato.

Los pacientes deben usar el spray nasal FLONASE a intervalos regulares como se indica ya que la efectividad depende del uso regular. Puede ocurrir una disminución de los síntomas nasales tan pronto como 12 horas después de comenzar la terapia con FLONASE. Los resultados de varias pruebas clínicas indican mejorías estadísticamente significativas después de uno o dos días de tratamiento; sin embargo, puede que no se logre todo el beneficio del spray nasal FLONASE hasta que el tratamiento se haya administrado por varios días. El paciente no debe aumentar la dosis recetada, pero debe comunicarse con el médico si los síntomas no mejoran o si empeora la condición. Para el uso correcto del spray nasal y para lograr una mejoría máxima, el paciente tiene que leer y seguir cuidadosamente las instrucciones que acompañan el producto.

Interacciones de fármacos: En un estudio cruzado controlado con placebo realizado con ocho pacientes voluntarios saludables, la coadministración de una sola dosis de propionato de fluticasona para inhalación oral (1000 mcg, 5 veces la dosis intranasal máxima diaria) con dosis múltiples de cetoconazol (200 mg) a estado estable, resultó en un aumento en las concentraciones medias del pro-pionato de fluticasona, una reducción en la línea bajo la curva del cortisol plasmático y en ningún efecto en la excreción urinaria de cortisol. Esta interacción puede deberse a una inhibición del sistema de isoenzimas del citocromo P450 3A4 por el cetoconazol, que también es la ruta de metabolismo del propionato de fluticasona. No se han realizado estudios de interacción de fármacos con el spray nasal FLONASE, sin embargo, se debe ejercer cautela cuando se coadministra el propionato de fluticasona con un cetoconazol a largo plazo o cualquier otro inhibidor del citocromo P450 3A4.

Carcinogénesis, mutagénesis, deterioro de la fertilidad: El propionato de fluticasona no demostró potencial tumorígeno en ratones en dosis orales de hasta 1000 mcg/kg (aproximadamente 20 veces la dosis intranasal máxima recomendada diaria en adultos y aproximadamente 10 veces la dosis intranasal máxima recomendada diaria en niños a base de mcg/m2) por 78 semanas o en ratas en dosis inhaladas de hasta 57 mcg/kg (aproximadamente 2 veces la dosis intranasal máxima recomendada diaria en adultos y equivalente aproximadamente a la dosis intranasal máxima recomendada diaria en niños a base de mcg/m2) por 104 semanas.

El propionato de fluticasona no indujo mutación genética en células proca-rióticas o eucarióticas in vitro. No se detectó efecto clastógeno significativo en cultivo de linfocitos periféricos humanos in vitro o en pruebas de micronúcleos de ratones cuando se administraron a dosis altas por vía oral o subcutánea. Además, el compuesto no retrasó la división eritro-blástica en la médula ósea.

No se observó evidencia de deterioro de la fertilidad en estudios de reproducción realizados en ratas machos y hembras con dosis subcutáneas de hasta 50 mcg/kg (aproximadamente 2 veces la dosis intranasal máxima recomendada diaria en adultos a base de mcg/m2). El peso de la próstata se redujo significativamente con dosis subcutáneas de 50 mcg/kg.

Embarazo: ***Efectos teratógenos:*** Embarazo categoría C: Los estudios subcutáneos con ratones y ratas con 45 y 100 mcg/kg, respectivamente (aproximadamente equivalente a, y 4 veces la dosis intranasal máxima recomendada diaria en adultos a base de mcg/m2, respectivamente) revelaron caracteristicas de toxicidad fetal de compuestos corticosteroides potentes, incluyendo retraso en el crecimiento embrionario, onfalocele, fisura del paladar y

osificación cranial retrasada.

En el conejo, se observó reducción en el peso fetal y fisura del paladar después de dosis subcutáneas de 4 mcg/kg (menos que la dosis intranasal máxima recomendada diaria en adultos a base de mcg/m2).

Sin embargo, no se informaron efectos teratógenos con dosis por vía oral de hasta 300 mcg/kg (aproximadamente 25 veces la dosis intranasal máxima recomendada diaria en adultos a base de mcg/m2) de propionato de fluticasona al conejo. En este estudio no se detectó propionato de fluticasona en el plasma, consecuente con la baja biodisponibilidad establecida luego de la administración por vía oral. (Véase la sección FARMACOLOGIA CLINICA que aparece en la información completa sobre prescripción).

El propionato de fluticasona cruzó la placenta después de la administración por vía oral de100 mcg/kg a ratas, ó 300 mcg/kg a conejos (aproximadamente 4 y 25 veces, respectivamente, la dosis intranasal máxima recomendada diaria a base de mcg/m2).

No hay estudios adecuados y bien controlados en mujeres embarazadas. Se debe usar el propionato de fluticasona durante el embarazo sólo si los beneficios potenciales justifican el riesgo potencial al feto.

La experiencia con corticosteroides orales desde su introducción en dosis farmacológicas, en oposición a fisiológicas, sugiere que los roedores son más propensos a efectos teratógenos de los corticosteroides que los humanos. Además, debido a que hay un aumento natural en la producción de corticosteroides durante el embarazo, la mayoría de las mujeres requieren una dosis menor de corticosteroides exógenos y puede que muchas no necesiten tratamiento con corticoteroides durante el embarazo.

Madres lactantes: No se sabe si el propionato de fluticasona se excreta en la leche humana. Cuando se administró propionato de fluticasona titulado a ratas por vía subcutánea en dosis de 10 mcg/kg, (menos que la dosis intranasal máxima recomendada diaria en adultos a base de mcg/m2), se excretó radioactividad en la leche. Debido a que otros corticosteroides se excretan en la leche humana, hay que ejercer cautela cuando se administra el spray nasal FLONASE a mujeres lactantes.

Uso pediátrico: En pruebas clínicas en los E.U. se estudiaron quinientos (500) pacientes entre las edades de 4 a 11 años y 440 pacientes de 12 a 17 años con el spray nasal de propionato de fluticasona. No se ha establecido la seguridad y efectividad del spray nasal FLONASE en niños menores de 4 años.

Se ha demostrado que con el uso extendido los corticosteroides orales y, a un grado menos claro los corticosteroides inhalados o intranasales, tienen el potencial de causar una reducción en la velocidad de crecimiento de niños y adolescentes. Si un niño o adolescente en un tratamiento con corticosteroides parece mostrar supresión en el crecimiento, se debe considerar la posibilidad de que sean particularmente sensibles a este efecto de los corticosteroides (Véase PRECAUCIONES).

Uso geriátrico: Se ha tratado un número limitado de pacientes de más de 60 años (n=275) con el spray nasal FLONASE en estudios clínicos en y fuera de los EU. Aunque el número de pacientes es muy pequeño para permitir análisis separados de eficacia y seguridad, las reacciones adversas informadas en esta población fueron similares a las informadas por pacientes más jóvenes.

REACCIONES ADVERSAS: En estudios controlados en los E.U. más de 3300 pacientes con rinitis alérgica de temporada, alérgica permanente o no alérgica permanente recibieron tratamiento intranasal con propionato de fluticasona. En general, las reacciones adversas en los estudios clínicos han estado relacionadas principalmente con irritación de las membranas mucosas nasales y las reacciones adversas informadas por pacientes tratados con el vehículo en sí mostraron aproximadamente la misma frecuencia. Las quejas por lo general no interfirieron con el tratamiento. Menos del 2% de los pacientes en las pruebas clínicas descontinuaron el uso a causa de los eventos adversos; esta tasa fue similar para comparadores de vehículo placebo y el ingrediente activo.

No se informaron efectos secundarios de los corticosteroides sistémicos durante los estudios clínicos controlados de hasta 6 meses de duración con el spray nasal FLONASE. Sin embargo, si se exceden las dosis recomendadas o si las personas son particularmente sensibles o si se usa el spray nasal FLONASE en conjunto con la administración de otros corticosteroides, pueden ocurrir síntomas de hipercorticismo, p. ej., síndrome de Cushing.

La siguiente incidencia de reacciones adversas comunes (>3%, donde la incidencia en sujetos tratados con propionato de fluticasona excedió la del placebo) se basa en siete pruebas clínicas controladas en que 536 pacientes (57 niñas y 108 niños entre las edades de 4 a 11 años, 137 mujeres y 234 varones adolescentes y adultos) recibieron tratamiento con 200 mcg del spray nasal FLONASE una vez al día por más de 2 a 4 semanas y dos pruebas clínicas controladas en que 246 pacientes (119 mujeres y 127 varones adolescentes y adultos) recibieron tratamiento con 200 mcg del spray nasal FLONASE una vez al día por 6 meses. En la tabla también se incluyen los eventos adversos de dos estudios en que se trataron 167 niños (45 niñas y 122 niños entre las edades de 4 a 11 años) con 100 mcg del spray nasal FLONASE una vez al día por 2 a 4 semanas.

Experiencias adversas generales con incidencia >3% con propionato de fluticasona en estudios clínicos controlados realizados con el spray nasal FLONASE en pacientes de ≥4 años con rinitis alérgica de temporada o permanente

	Vehículo placebo (n=758) %	FLONASE® 100 mg una vez/día (n=167) %	FLONASE® 200 mg una vez/día (n=782) %
Dolor de cabeza	14.6	6.6	16.1
Faringitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Ardor nasal/ irritación nasal	2.6	2.4	3.2
Náuseas/vómitos	2.0	4.8	2.6
Síntomas de asma	2.9	7.2	3.3
Tos	2.8	3.6	3.8

Otros eventos adversos que ocurrieron en ≤3% pero ≥1% de los pacientes y que fueron más comunes con el propionato de fluticasona (de relación incierta con el tratamiento) incluyeron: sangramiento nasal, agua por la nariz, dolor abdominal, diarrea, fiebre, síntomas parecidos a los de la influenza, molestias y dolores, mareos, bronquitis.

Observadas durante la práctica clínica: Además de los eventos adversos informados en las pruebas clínicas, se han identifi-cado los siguientes eventos durante la postaprobación del uso del propionato de fluticasona en la práctica clínica. Como se informan voluntariamente de una población de tamaño desconocido, no se pueden hacer estimados de frecuencia. Se han escogido estos eventos para inclusión debido a la seriedad, frecuencia con que se informan, conexión causal con el propionato de fluticasona, ocurrencia durante las pruebas clínicas o una combinación de estos factores.

Generales: Reacciones de hipersensibilidad, incluso angio-edema, erupción cutánea, edema de la cara y la lengua, prurito, urticaria, broncospasmo, sibilancias, disnea y anafiláxi/reacciones anafilactoides, que en raras ocasiones fueron severas.

Oído, nariz y garganta: Alteración o pérdida del sentido del gusto y/o olfato y, rara vez, perforación del tabique nasal, úlcera nasal, dolor de garganta, irritación y resequedad de la garganta, tos, ronquera y cambios en la voz.

Ojos: Resequedad e irritación, conjuntivitis, visión borrosa, glaucoma, aumento en la presión intraocular y cataratas.

SOBREDOSIS: Una sobredosis crónica con el spray nasal FLONASE puede tener como resultado signos/síntomas de hipercorticismo (véase PRECAUCIONES). Voluntarios saludables humanos toleraron bien la administración intranasal de 2 mg (10 veces la dosis recomendada) de propionato de fluticasona dos veces al día por 7 días. Se han estudiado dosis orales sencillas de hasta 16 mg en voluntarios humanos sin que se hayan informado efectos tóxicos agudos. Se toleraron bien las dosis repetidas de hasta 80 mg diarios por 10 días en voluntarios y dosis repetidas orales de hasta 10 mg diarios por 14 días en pacientes. Las reacciones adversas fueron de severidad de leve a moderada y las incidencias fueron similares en grupos de tratamiento activo y con placebo. Una sobredosis aguda con esta dosis es poco probable ya que un frasco del spray nasal FLONASE contiene aproximadamente 8 mg de propionato de fluticasona.

La dosis letal media oral y subcutánea en ratones y ratas fue de >1000 mg/kg (>20000 y >41000 veces, respectivamente, la dosis intranasal máxima recomendada diaria en adultos y >10000 y>20000 veces, respectivamente, la dosis intranasal máxima recomendada diaria en niños a base de mg/m2).



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Artículos de Revisión:

Infant Hearing Loss: The Necessity for Early Identification

Charles L. Harney, MA

Abstract:

There has been controversy in the health professions about the necessity for newborn infant hearing screening. It is well accepted that patient history or a birth that places the infant in the high-risk registry (HHR) can identify 50% of all i'nfants born with permanent bilateral hearing loss. Two major factors which have been cited as reasons for not screening the well-baby nursery have been poor cost effectiveness and the lack of documentation as to the benefits derived from early identification and intervention. Recent technological developments and published data are presented which indicate that economical well-baby hearing screening can be done in any setting, and that the language acquisition of the infant is permanently affected if the intervention is not done in the first six months after birth.

Key words: Infant hearing, screening, early intervention.

In 1994 The Joint Committee on Infant Hearing (1) issued a position statement that recommended that all infants with hearing loss be identified by three months of age and receive intervention by six months of age. This was done in support of the National Institute of Health Consensus Statement (2) outlining the problems' associated with infant hearing loss and the consequences of late identification and intervention. In a key article published in the Journal of Pediatrics (3) Bess & Paradise questioned the viability of universal newborn hearing screening (UNHS). Their critique has been widely quoted as a reason for not initiating a hearing-screening program in the well-baby nursery.

There were three major concerns of the two authors. The viability of screening every infant to be born in the United States and the cost effectiveness of the program were questioned. In particular, there was a lack of documentation that identification and intervention for the hearing-impaired child at or before six months of age would result in any significant benefit over identification at a later date.

The process of identification and intervention

Ten out of every 100 births fall into the HHR. The number of hearing-impaired infants in this category makes up 50% of all newborns that have permanent bilateral hearing loss (4). The prevalence of permanent hearing loss in the newborn population is 3:1000 (5). For that reason it has long been accepted that these infants must receive a hearing screening with either otoacoustic emissions (OAE) or auditory evoked potentials (AER) before discharge. OAEs are sounds produced by the outer hair cells of the cochlea, and registered in the ear canal of the infant, in response to low level acoustic stimuli. They can only be obtained if the middle ear and cochlea have hearing within normal limits.

When an infant fails these tests he is referred to an audiologist who administers a series of evaluations th'at assess the middle ear, cochlea and the central auditory pathways. When permanent hearing loss is identified the audiologist fits the infant with hearing aids and refers the parents to a speechlanguage pathologist who begins the long process of speech therapy. Since a significant number of hearing-impaired infants have additional disabilities other specialists such as otolaryngologists, developmental pediatricians and pediatric neurologists may also attend to the child.

The cost of identifying infants with prelingual hearing loss may be substantial. Hearing screening in the well baby nursery averages $25.00/ infant (reference) and in the HHR may be as much as $100.00. A full audiological work-up will costs $300.00 with

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additional expenses when other specialists are called in for consultation. However, these initial costs are nothing compared to the costs of educating a hearing-impaired child. There is an additional loss in revenues because few hearing-impaired children can hope to function academically at the same level as their age group.
In fact, the average deaf childs' academic achievement does not go past the fourth grade level (6). The cost to society has been estimated to be as much as $1,000,000.00 per each hearing-impaired child (6). It is for this reason that successful implementation of the initial program of identification is critical to reduce the long-term costs to society.

What determines a successful newborn hearing screening program is the sensitivity and specificity of the tests used to detect hearing loss, a low (<4%) false positive rate, the follow-up of all infants that fail the initial screening, and timel intervention for those infants when hearing los confirmed.

Language ability and early identification

In 1998, Yoshinaga-Itano and her associates (7) published a landmark study that demonstrated the positive effects of early intervention for a group of 150 hearing-impaired children ranging in age from 13 months to 36 months. The children were divided into two groups, those that had been identified as hearing-impaired and intervention begun before six months of age (Group 1), and those where intervention occurred after six months of age (Group 2). Both groups had children drawn from the HHR and the well-baby nursery. The groups where matched for hearing loss, economic status, multiple disabilities and further divided into normal and low cognition groups for additional analysis. Language comprehension and expression was scored utilizing two scales of the Minnesota Child Development Inventory (MCDI) test.

The results of this study were significant in several ways:

1. The infants in Group 1 with normal cognition scored normal for their chronological age in language comprehension and expression.

2. All infants in Group II scored well below normal in the tests of language expression and comprehension.

3. Infants in Group 1 with low cognition scores were at the same language level as those infants with normal cognition in Group 2.

4. Group 2 was further divided into four more groups with identification of hearing loss at 7-12 months,'13-18 months, 19-24 months and 25-30 months. When tested at 36 months no significant difference in language ability was found among the five sub-groups.

The results demonstrated that early identification is not justified unless early intervention is also present.

The current status of UNHS

In the last five years only two small states have developed successful UNHS programs. Hawaii and Rhode Island currently screen 98% or more of all infants born in those states and have a median age of intervention of 5-6 months (8). Virginia, Colorado, Texas, Arizona and others have implemented individual hospital programs (9). However, although highly successful in the identification of hearing loss in the newborn population these hospital-based programs have failed to adequately document the follow-up of those infants who failed the initial screening (10).

In Puerto Rico, screening for infants who fall into the HHR is being done at several hospitals. But, at the pediatric hospital in Rio Piedras, only one audiologist is available to administer the full battery of tests. That individual estimates that the time of intervention exceeds eight months in the majority of infants who have been confirmed with permanent bilateral sensory hearing loss (11). This means that the money expended in the identification of these infants has been wasted.

The use of new technology

In 1998 Otodynamics Inc. introduced a small hand-held OAE screening unit that can be carried in a large pocket (12). This was quickly followed by other manufacturers with similar units. These units can screen newborn hearing in any setting with ambient noise areas not exceeding that of a physicians' office. The test takes only a few seconds for each ear. The development of these units means that all infants and children at any age can be routinely screened for hearing loss.

Summary:

The necessity for early identication of hearing loss has been objectively confirmed. The technology is available so that all infants with prelingual hearing loss can be identified and early intervention initiated. The delay in identification and remediation of childhood hearing loss can no longer be justified from a medical, moral or

legal reason. All pediatricians and family physicians should understand the personal and financial risks involved with failure to have infants who fall into the HHR referred for a hearing screening test.

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Artículos de Revisión:

Allergic and Non-Allergic Rhinitis

Mariano González Diez, M.D., FACS

Introduction

The definition of bronchial asthma has plagued chest physicians and allergists for years, so it is not surprising that the definition and classification of rhinitis, involving etiologic criteria (infectious, allergic), has caused even more confusion. There is no universally accepted system for the definition, classification or the terminology of rhinitis. Use of different terms for the same disease and of the same term for different diseases has, in the past, made reports on rhinitis confusing to read and difficult to compares

In daily work, the diagnosis is of importance for proper counselling, as a guide to therapy, and is necessary for unambiguous communication between clinicians. In the presentation below, we have made the classification simple in order to ensure that a patient will be given the same diagnosis when examined by different doctors (Table 1.1).[1]

Table 1.1. Simple classification of rhinitis.

1. Infectious (purulent) rhinitis
2. Seasonal allergicrhinitis = hay fever = pollinosis
3. Perennial allergic rhinitis
4. Perennial non-allergic rhinitis (eosinophilic or non-eosinophilic)

Rhinitis or rhinopathy?

The term 'rhinitis' implies an inflammatory disease of the nasal mucous membrane. Demonstration of local inflammation is, however, not practical. Clinical diagnoses are based on the presence of symptoms: itching, sneezing, discharge and blockage.

As these symptoms may occur without inflamation, 'rhinopathy' is, strictly speaking, a more correct term - but it is rarely used.

Anatomic abnormalities

All patients with chronic nasal symptoms need an ENT examination in order to exclude anatomic abnormalities. The combined use of an endoscopic examination and a CT-scan imaging (when necessary and when possible) gives a much better presentation of anatomic and mucosal abnormalities than do simple rhinoscopy and plain x-ray examination.

Infectious or non-infectious?

Often, a diagnosis of infectious rhinitis is supported by associated symptoms from the throat and the lower airways, but it may occasionally be confused with non-infectious rhinitis. As a matter of clinical routine, a diagnosis of viral or bacterial disease is not based on identification of the specific microorganism. The distinction made is between purulent and non-purulent rhinitis based on the macroscopic character of the nasal discharge (cloudy and milky/colored, or clear and watery/mucoid), preferably supported by microscopy (+ neutrophilia). The reliability of this sign, however, is not absolute. Neutrophilia can be caused not only by viral and bacterial infection but also by exposure to air pollution.[2]

Allergic or non-allergic?

The diagnosis of inhalant allergy can usually be agreed on when history, physical examination, and skin test/RAST results are combined. This is not the case with food allergy, which is a controversial topic. Food allergy as a cause of isolated rhinitis is debatable; but, as a part of documented IgE-mediated allergy to foods, nasal symptoms may occur, especially in children.[3]

The term 'vasomotor rhinitis' is often used for non-infectious, non-allergic rhinitis. However, there is no evidence for the existence of a 'vasomotor pathogenesis'.
In addition, it is confusing that the term is presently used with different meanings in Europe (non-allergic rhinitis) and in North America (non-allergic non-eosinophilic rhinitis).
For these reasons, it may be wise to drop the term 'vasomotor rhinitis', as it confuses more than it clarifies, and

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it gives a false impression of a well-defined pathogenesis.[4]

Seasonal or Perennial

Seasonal allergic rhinitis is a generally accepted term for pollinosis or hay fever. But pollen allergy is often perennial in the tropics, and a seasonal increase of symptoms can be caused by allergy to mites and molds in temperate zones. Seasonal refers to short exposures lasting for a few months, while perennial implies continuous or intermittent exposure with chronic or periodic symptoms.[5]

The symptomatology of seasonal rhinitis is characterized by sneezing, whereas in perennial rhinitis congestion often dominates.[6]

Eosinophilic or non-eosinophilic?

Non-allergic rhinitis is a heterogenous syndrome consisting of two main groups. One is characterized by nasal secretion eosinophilia, frequent occurrence of nasal polyps, hyperplastic sinusitis, non-allergic or intrinsic asthma, intolerance to acetylsalicylic acid and other NSAID preparations.[7]

Most clinicians do not examine nasal smears and are not familiar with microscopic evaluation.
In addition, the specificity and reproducibility of this test has not been properly analyzed. Serial examination seem to be necessary for a reliable characterization of the disease. The classificatio of patients with non-allergic rhinitis into an eosinophilic and a non-eosinophilic group is, therefore, not entirely suitable for clinical diagnosis.
The presence of eosinophils usually portbnds a response to glucocorticosteroids.[8]

Other causes of chronic nasal symptoms

Rhinitis medicamentosa develops after prolonged use of vasoconstrictor sprays. Nasal congestion can be caused by medication with antihypertensives and psychosedatives, which act as alpha-adrenoceptor antagonists.[9]

Pregnancy is, in a number of cases, associated with persistent nasal blockage and sinusitis symptoms, which disappear after delivery (Table 1.2).

Congenital choanal atresia can be a cause of nasal obstruction, with discharge, in infants. A foreign body is much more common at that age. Enlarged adenoids are a frequent cause of mouth breathing. Septal deviation is another well-known cause of nasal obstruction, often bilateral (S-shaped deviation).
A nasal blockage, developing in an adult, cannot be ascribed exclusively to septal deviation, unless the patient has had a traumatic fracture.
However, the swollen mucous membrane of rhinitis can make a septal deviation clinically significant, so this type of patient has a combined problem.[10]

Table 1.2.
Other causes of nasal symptoms.

Mechanical factors
Septal deviation
Nasal polyps
Foreign body
Tumors of nose and paranasal sinuses
Tumors of the nasopharynx
Congenital choanal atresia
Meningocele/Encephalocele
Adenoidal hypertrophy
Infections
Viral infection (common cold)
Bacterial infection
Sinusitis
Leprosy
Immunodeficiency
Primary ciliary dyskinesia
Miscellaneous
Rhinitis medicamentosa
Pregnancy
Antihypertensives
Wegener's granulomatosis
Cystic fibrosis
Leak fo cerebrospinal fluid

Malignant tumors in the nose, paranasal sinuses and nasopharynx, and Wegener's granulomatosis usually start with uncharacteristic symptoms. A first diagnosis of 'perennial non-allergic rhinitis' is not uncommon in these cases, and nasal endoscopy and imaging of paranasal sinuses are obligatory in patients with unilateral symptoms, hemorrhagic secretions or pain.[11]

A practical approach to the diagnosis of rhinitis

First, exclude other diseases and structural abnormalities. Then make a distinction between infectious and non-infectious disease (history, character of discharge), and separate allergic from non-allergic patients on the basis of history and allergic testing. Subclassification of the non-allergic patients into an eosinophilic and a non-eosinophilic group is helpful, as it relates to the responsiveness to pharmacotherapy. When repeated sampling and microscopy of a nasal smear are not feasible, the alternative is a therapeutic trial with, e.g., a steroid spray.

The case history, preferably supported by daily symptom recording for 2 weeks in perennial cases, allows a characterization of the patient according to the most prominent symptom. 'Sneezers'

(sneezing and discharge), 'nose-blowers' (watery discharge), and Iblockers, (nasal blockage) show varying response to drugs, e.g. antihistamines, and require different therapies.

Conclusion:

The different types of rhinitis are at present poorly defined and the limits between 'normal' and disease' are fluid. Rhinitis can be infectious (purulent), allergic or non-allergic. The latter is a heterogenous syndrome consisting of at least two main groups, an eosinophilic and a non-eosinophilic: a distinction which is not entirely suitable for clinical practice.

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Rhinosinusitis

*Factors and Classifications**

*The AAO-HNS Rhinosinusitis Task Force recognizes that there are no true pathologic classifications for adult rhinosinusitis.

The following classifications are based on committee consensus. It is important that all physicians utilize standard terminology when describing various forms of rhinosinusitis. This will provide a strong communication's framework for clinicians and researchers and will promote progress toward the improved treatment of rhinosinusitis.

Factos associated with the diagnosis of chronic rhinosinusitis

Major factors
- Facial pain/pressure
- Facial congestion/fullness
- Nasal obstruction/blockage
- Nasal discharge/purulence/ discolored postnasal drainage
- Hyposmia/anosmia
- Purulence in nasal cavity on examination

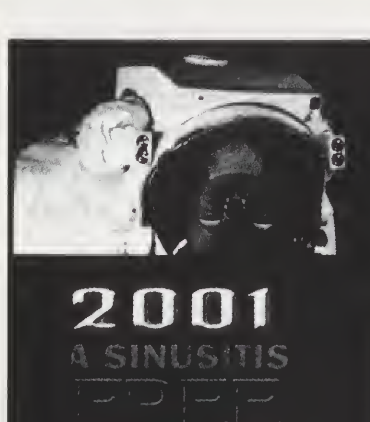
Minor factors
- Headache
- Fever (nonacute)
- Halitosis
- Fatigue
- Dental pain
- Cough
- Ear pai/pressure/fullness

YOUR NAME HERE

CLASSIFICATIONS OF ADULT RHINOSINUSITIS

Classification	Duration	Strong history	Include in differential	Special notes
Acute	≤ 4 weeks	≥ 2 major factors, 1 major factor and 2 minor factors, or nasal purulence on examination	1 major factor or ≥ 2 minor factors	Fever or facial pain does not constitute a suggestive history in the absence of other nasal signs or symptoms. Consider acute bacterial rhinosinusitis if symptoms persist for > 10 days, or in presence of symptoms out of proportion to those typically associated with viral infection.
Subacute	4 - 12 weeks	Sames as chronic	Same as chronic	Complete resolution after effective medical therapy
Recurrent acute	≥ 4 episodes per year, with each lasting ≥ 7 to 10 days and absence of intervening signs and symptoms of chronic rhinosinusitis	Same as acute		
Chronic	≥ 12 weeks	≥ 2 major factors, 1 major factor and 2 minor factors, or nasal purulence on examination	1 major factor or ≥ 2 minor factors	Facial pain does not constitute a suggestive history in the absence of other nasal signs or symptoms.
Acute exacerbations of chronic	Sudden worsening of chronic rhinosinusitis, with return to baseline after treatment			

Lanza DC., Kennedy DW. et al. Adult Rhinosinusitis Task Force Committee Meeting. Otolaryngology-Head and Neck Surgery 1997; 117; S4-S5.



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Sinus Pain

Allergic rhinitis, sinusitis, and rhinosinusitis

What is rhinitis?

Inflammation of the nasal mucous membrane is called *rhinitis.* The symptoms include sneezing, runny nose, and itching, caused by irritation and congestion in the nose. There are two types: *allergic rhinitis* and *non-allergic rhinitis*

Allergic rhinitis: This condition occurs when the body's immune system over-responds to specific, non-infectious particles such as plant pollens, molds, dust mites, animal hair, industrial chemicals (including tobacco smoke), foods, medicines, and insect venom. Essentially, during an allergic attack, antibodies, primarily immunoglobin E *(IgE),* attach to mast cells in the lungs, skin, and mucous membranes. Once IgE connects with the mast cells, a number of chemicals are released. One of the chemicals, histamine, opens the blood vessels and causes skin redness and swollen membranes. When this occurs in the nose, sneezing and congestion are the result.

Seasonal allergic rhinitis or *hayfever* occurs in late summer or spring. Hypersensitivity to ragweed, not hay, is the primary cause of seasonal allergic rhinitis in 75 percent of all Americans who suffer from this seasonal disorder. People with sensitivity to tree pollen have symptoms in late March or early April; an allergic reaction to mold spores occurs in October and November as a consequence of falling leaves.

Perennial allergic rhinitis occurs year-round and can result from sensitivity to pet hair, mold on wall paper, house plants, carpeting, and upholstery. Some studies suggest that air pollution such as automobile engine emissions can aggravate allergic rhinitis. Although bacteria is not the cause of allergic rhinitis, one medical study found a significant number of the bacteria *Staphylococcus aureus* in the nasal passages of patients with year-round allergic rhinitis, concluding that the allergic condition may lead to higher bacterial levels, thereby creating a condition that worsens the allergies.

Non-allergic rhinitis: This form of rhinitis does not depend on the presence of IgE and is not due to an allergic reaction. The symptoms can be triggered by cigarette smoke and other pollutants as well as strong odors, alcoholic beverages, and the cold. Other causes may include blockages in the nose, a deviated septum, infections (in children), and over-use of medications such as decongestants.

Rhinosinusitis – Clarifying the relationship between the sinuses and rhinitis

Recent studies by otolaryngologist–head and neck surgeons have sought to better define the association between rhinitis and sinusitis. They have concluded that sinusitis is often preceded by rhinitis and rarely occurs without concurrent rhinitis. The symptoms, nasal obstruction/discharge and loss of smell occur in both disorders. Most importantly, computed tomography (CT scan) findings have established that the mucosal linings of the nose and sinuses are simultaneously involved in the common cold (previously, thought to affect only the nasal passages). Otolaryngologists, acknowledging the inter-relationship between the nasal and sinus passages, now refer to sinusitis as rhinosinusitis.

(OVER)

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Sinus Pain

The catalyst relating the two disorders is thought to involve nasal sinus overflow obstruction, followed by bacterial colonization and infection. The resulting nasal obstruction leads to acute, recurrent, or chronic sinusitis; conversely, chronic inflammation due to allergies can lead to obstruction and subsequent sinusitis.

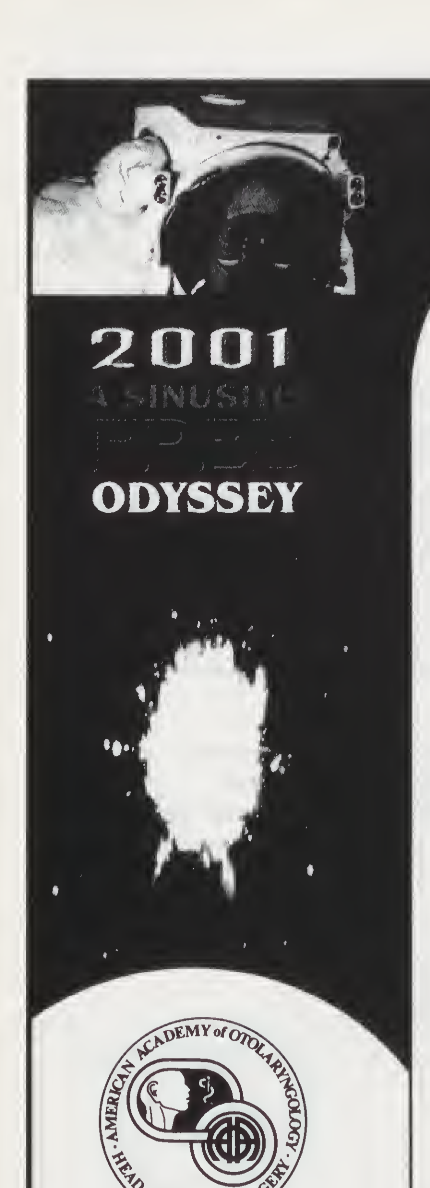
Other medical research has supported the close relationship between allergic rhinitis and sinusitis. In a retrospective study on sinus abnormalities in 1,120 patients (from 2 to 87 years of age), thickening of the sinus mucosa was more commonly found in sinusitis patients during July, August, September, and December, in which pollen, mold, or viral epidemics are prominent. A review of patients (four to 83 years of age) who had surgery to treat their chronic sinus conditions revealed that those with seasonal allergy and nasal polyps are more likely to experience a recurrence of their sinusitis.

Patients who suffer from recurring bouts of allergic rhinitis should observe their symptoms on a continuous basis. If facial pain or a green-yellowish nasal discharge occur, a qualified ear, nose, and throat specialist can provide appropriate sinusitis treatment.



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Sinus Pain

Ear, Nose, and Throat Specialists Advise Americans That Chronic Sinusitis Can Be Successfully Treated

Otolaryngoloists (ear, nose, and throats specialists) proclaim March 2001 as Sinus Pain Awareness Month – An Odyssey to Effective Diagnosis and Treatment – and offer tips for millions with this respiratory disease

Alexandria, VA – It is ironic that in the year that Stanley Kubrick's classic movie, *2001, A Space Odyssey,* celebrates our outreach to the stars, more than 37 million Americans will remain earthbound because they suffer from sinusitis, one of this nation's leading chronic medical disorders. Having chronic sinusitis leads to debilitating pain and a decline in quality of life. The upper respiratory disorder also eliminates one from consideration to the astronaut program.

Although patients with a chronic sinus condition will never reach the stars, they do have the opportunity to find effective diagnosis and treatment for their disorder. The nation's 10,000 ear, nose, and throat specialists, members of the American Academy of Otolaryngology–Head and Neck Surgery and the American Rhinologic Society, have designated March, 2001, as *Sinus Pain Awareness Month.* This health observance period asks that Americans who believe they are suffering from a cold or allergy to seek specialty care to determine if their symptoms are from sinusitis, which unlike most common respiratory ailments, is treatable with a prescription antibiotic.

In March, we ask Americans to remember that:

- ▲ Chronic sinusitis, defined as four sinus infections in a year, is the most persistent medical condition affecting Americans of both sexes and all ages, city dwellers, and farm residents.
- ▲ Elderly Americans should be aware of the dangers of mixing various medications in treating sinusitis; children with sinusitis may cough more than adults. Those suffering from allergic rhinitis (hay fever) have a higher propensity for sinus disorders than the general population.
- ▲ As the incidence of sinusitis continues to increase, so do the economic costs of this medical disorder. Outlays for pharmaceutical products and physician visits, coupled with loss of work, suggest that seeking appropriate treatment immediately, may defray the dollar costs associated with this disorder.
- ▲ Those with chronic sinusitis report more pain, depression, and fatigue in their lives than do patients with angina, chronic heart disease, or back pain.

The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) outlines the cause, diagnosis, and treatment for sinus disorders on its website, **www.entnet.org.** The same information is contained in a leaflet, "Doctor, what is sinusitis," which is available at no cost by sending a stamped, self-addressed business envelope to Sinus Pain, American Academy of Otolaryngology–Head and Neck Surgery, One Prince Street, Alexandria, VA 22314-3357. Visit **www.entnet.org** or **www.american-rhinologic.org** for additional information.

Editor's Note: Sinus Pain Awareness Month appears in the 2001 Health Observances & Recognition Days Calendar published by the American Hospital Association. For additional information or an interview with an otolaryngologist, contact Ken Satterfield at 703-519-1563 or email **sinuspain@entnet.org.**

FOR MORE INFORMATION:
See your otolaryngologist or contact the American Academy of Otolaryngology—Head and Neck Surgery
One Prince Street, Alexandria, VA 22314-3357 U.S.A.
phone: 1-703-836-4444
fax: 1-703-683-5100
online: www.entnet.org

This public education campaign supported in part by a grant from Ortho-McNeil Pharmaceutical, makers of LEVAQUIN® (levofloxacin).



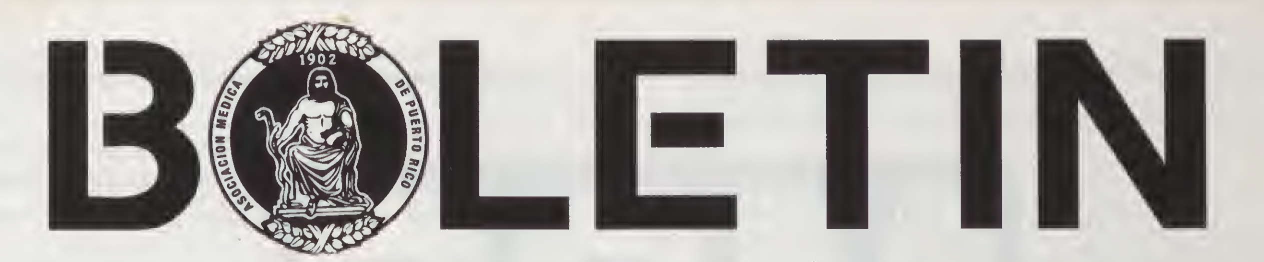
CONTENIDO

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ABRIL - MAYO - JUNIO - JULIO - AGOSTO

SEPTIEMBRE - OCTUBRE - NOVIEMBRE - DICIEMBRE



Instrucciones para los Autores*

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica. Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos, no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicara únicamente en la revista. Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquinilla a doble espacio; por un sólo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre de autor(es) y su grado (ej.: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben orgonizarse bajo los siguientes encabezamientos: introducción, Materioles y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes o estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicomentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea se usorá con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse los toblos a solo aquellos que contribuyan al mejor entendimiento del manuscrito.

Ilustraciones

Las fotografías y microfotogrofías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de lo ilustroción.

Resumen

Un abstrocto no moyor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren lo substancio del artículo y la exposición del problema, métodos, resultados y conclusiones.

Referencias

Los referencios deben ir numeradas sucesivamente de acuerdo a su aporición en el texto. Los números deben oporecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publico la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuoción.

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Cartas al Editor

Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquinilla a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

ARTICULO DEBERA SER ACOMPAÑADO POR UN "DISKETTE".

**Estas "Instrucciones para los Autores" son de acuerdo a las normas establecidos por el Comité Internacional de Editores de Revistas Médicas en sus "Requisitos Uniformes para Manuscritos Sometidos a Revistas Bio-Médicas".*

Instructions to Authors*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understandig that is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board ond the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been at a rneeting the place and date should be given.

The manuscripts should start with a brief introductory parograph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by heading in capitai letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Materiols and Methods, Result if indicated, Discussion, Summory in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names ofdrugs should be used; trade names my also be given in parenthesis, if desired, metric units of measurement should be used preferentially.

Tables

These should be typed on seporote sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The languoge used in the tables must be the same os thot of the article. Include only those tables which will enhance the understonding of the article. They should supplement, not duplicate the text.

Figures

Photogrophs and photomicrographs shoul be submitted as glossy prints (unmounted) or slides. They should be labeled in the back with the name of the outhors ond figure number (Arobic) and the top should be indicoted. Legend to the figures should be typed on o separote sheet.

Summary

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

References

These should be numbered serially as they oppeor in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should obe abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

1. For periodicals: Surname and initials of author(s), title of article, name of journol, year, volume, pages. For example:
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2. For books when the authors of the cited chapter is ot the same time the editor: Surname and initials of author(s), title, edition, city, publishing house, year ond page. For example: Keith JD, Rowe RD, Vlad P: Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 789

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   Olley PM: Cardiac arrythmias: In: Keith JD, Rowe RD, Vlad P. Eds. Heart disease in infancy and childhood, 3d Ed. New York, MacMillon, 1978, 275-301

Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

ARTICLES SHOULD BE ACCOMPANIED WITH A "DISKETTE".

**The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requierements for Manuscripts Submitted to Biomedical Journals".*



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